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PHYSIOLOGICAL REVIEWS

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AFFERENT PATHS FOR VISCERAL REFLEXES

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Although the control which the nervous system exerts over the activity of the viscera has furnished problems for numberless investigations, attention has been directed almost exclusively to the efferent side of the visceral nervous system. Very little has been done in a systematic way toward a study of the afferent fibers to the viscera, their course through the sympathetic nervous system and cerebrospinal nerves, and the connections which they make in the central nervous system. Visceral reflexes have been extensively investigated but as a rule the sources of the afferent impulses which are capable of eliciting these responses have been mentioned only incidentally. Probably the first attempt to attack this problem in a systematic manner is that now being made by Carlson and Luckhardt (1) and these investigators have had their attention diverted to some extent by a surprising number of important observations on the efferent side of the visceral nervous system.

In a broad sense visceral reflexes may be said to include *a*, the response of smooth and cardiac muscle and glandular tissue to stimulation of visceral afferent fibers; *b*, the response of these same effectors to the stimulation of somatic afferent fibers; and *c*, somatic responses initiated through irritation of the viscera or visceral nerves. Of this third group we shall consider only those which fall under the general head of respiratory reflexes. Other skeletal reflexes which may be initiated by stimulation of the viscera or visceral nerves have been considered along with the related literature in a recent paper by Carlson and Luckhardt (2).

Lennander's (3) idea that all visceral pain was mediated through the parietal peritoneum was definitely disproven by Neumann (4), (5), (6) who has also given a good review of the earlier literature on visceral sensibility. The subject has been rather extensively investigated in

recent years (7), (8), (9), (10), (11), (12), (13), (14), (15), (16), (17), (18), (20). We now know that afferent impulses of visceral origin may appear in consciousness as painful sensations and that at least in the stomach and large intestine there is also a crude form of temperature sensibility. But the majority of the afferent impulses from the viscera never rise into consciousness at all but expend themselves in the production of reflexes, some of which will be described in the following sections of this paper.

The most detailed and accurate study of the distribution of sensory fibers from the spinal nerves through the sympathetic system is that of Head (21) based on a comparison of the areas of referred pain in visceral disease. He concluded that sensory fibers from the heart terminated in segments 1, 2 and 3T. of the spinal cord; those from the lungs in 1, 2, 3, 4 and 5T.; from the stomach in 6,7,8 and 9T.; from the small intestine and colon in 9, 10, 11, 12 T; from the rectum in 2, 3 and 4 S.; from the liver, 7, 8, 9, 10 T.; from the kidney and ureter, 10, 11, 12 T.; from the bladder, 11, 12 T., 1L and 2, 3 and 4 S.; from the prostate in 10, 11, 12 T., and 1, 2 3 S.; from the testis and ovary, 10 T.; from the uterus, 10, 11, 12 T., 1 L., and 2, 3 and 4 S. As pointed out by Thorburn (22), Head's lower thoracic and upper lumbar areas are probably placed one segment too high. If these corrections are made Head's results fall in line with what anatomical information we have concerning the distribution of these fibers.

Some of the sensory fibers entering the sympathetic nervous system from the cerebrospinal nerves are of relatively large size and their course is quite easily followed (23), (24), (25), (26). Contrary to what one would expect from Head's work Langley and Anderson (27) were not able to trace any medullated sensory fibers from the sacral nerves to the internal generative organs. Ranson and Billingsley (28) have studied the distribution of these large afferent fibers in the sympathetic nervous system of the cat and have obtained results which are in general agreement with those of previous investigators.

The largest numbers of these fibers enter the sympathetic system through the seventh to the tenth white rami inclusive. The large sensory fibers from the upper three white rami can be traced upward through the sympathethic trunk and stellate ganglion to be distributed to the heart and lungs. None are present in the trunk in the cervical region and very few at the level of the fourth thoracic vertebra. Only a few are found in the fourth and fifth white rami. Those from the sixth and lower white rami run downward in the smypathetic trunk and through the splanchnic nerves to the abdominal viscera. Similar large sensory

fibers are found in the visceral branches of the sacral nerves for the pelvic viscera, and others can be traced downward in the vagus as far as the pulmonary branches. No large myelinated fibers are found in the esophageal plexus or in the gastric branches of the vagus (29).

Langley (24) found difficulty in correlating the degree of sensitiveness of different parts of the sympathetic system, as evidenced by the ease with which their stimulation would produce general reflexes, with the number of large myelinated fibers they contained. We now know that among the visceral afferent fibers there are included in addition to the large, also medium and small myelinated and many unmyelinated fibers. How far the distribution of the large myelinated and the other visceral sensory fibers correspond is a matter for future investigation. It is known however that the afferent fibers to the stomach in the vagus are for the most part unmyelinated and are accompanied by no large myelinated fibers.

Since 1896 when Dogiel (30) described a sensory type of sympathetic ganglion cell there has been a great deal of confusion concerning the location of the cells of origin of the visceral afferent fibers. Degeneration experiments with the Marchi method lead Michailow (31) to support Dogiel's thesis that sensory fibers arising from sympathetic ganglion cells terminate in the form of pericellular plexuses about spinal ganglion cells. But to anyone familiar with the Marchi stain Michailow's figures are far from convincing. Some observations of Kuntz (32) might possibly be interpreted as favoring Dogiel's theory. But the balance of evidence is against it and indicates that all visceral afferent fibers have their cells of origin in the cerebrospinal ganglia (33), (34), (35), (36). The evidence on this point has been presented in some detail by Ranson and Billingsley (37).

The afferent fibers of the vagus, the location of their cells of origin and their peripheral distribution have recently been studied by a number of investigators (38), (39), (40), (41), (42), (29). These fibers, which are distributed to the thoracic viscera, the stomach and perhaps to some of the other abdominal organs have their cells of origin in the nodose ganglion. On entering the brain stem they run in the tractus solitarius and terminate in the nucleus associated with that tract. From cells in the nucleus of the tractus solitarius fibers arise which ascend and descend in the reticular formation of the brain stem and make connections with the various visceral motor nuclei. Many visceral reflex arcs therefore consist of three neurons: *a*, a primary afferent neuron of the vagus; *b*, a secondary afferent neuron with its cell in the nucleus of the tractus

solitarius; *c*, a visceral efferent neuron with cell of origin in one of the nuclei of the visceral efferent column (35).

Concerning the paths within the central nervous system by which afferent impulses reach the centers for the various visceral reflexes, very little is known and such observations as bear on this topic can best be mentioned in connection with the particular reflexes concerned. At present our information concerning the afferent paths for visceral reflexes, must be largely based on rather unsystematic observations concerning the sources of the particular afferent impulses that are able to initiate the various reflexes and concerning the peripheral nerves which convey these impulses to the central nervous system. These observations are widely scattered through the literature and are rather difficult to present in condensed form. Because of limits of time and space we have confined our attention to the respiratory, cardiovascular, and gastro-intestinal reflexes.

RESPIRATORY REFLEXES. *The respiratory center.* The respiratory movements involve the coördinated activity of many widely separated groups of muscles; and this coördination is provided for by a respiratory center situated in the medulla beneath the caudal part of the fourth ventricle. The center is said by von Bechterew (43), who gives a good account of the literature on this subject, to be located in the reticular formation lateral to the root-fibers of the hypoglossal nerve. Recent work tends to confirm the generally accepted theory that the respiratory center has its own automatic rhythm (44), (45), (46), (47). Some investigators have seen what they interpreted as respiratory movements in decapitated young animals, possibly indicating the presence of respiratory centers in the spinal cord, and have assumed that the failure of respiration after transection of the upper part of the spinal cord was due to the stimulation of inhibitory fibers by the section. Stewart and Pike (45) obtained evidence of rhythmic activity in the spinal respiratory centers of a young cat in which cerebral anemia had thrown the bulbar centers out of action. But Trendelenburg (48) has shown that respiratory movements ceased when the conduction of impulses from the medulla to the spinal cord was interrupted by the application of cold without stimulation of inhibitory fibers. He concludes that the respiratory center is in fact located in the medulla and that the isolated spinal centers retain no capacity for initiating rhythmic respiratory movements.

The medulla and spinal cord are however not the only portions of the central nervous system concerned in respiration. Lewandowsky (49), Nikolaides (50) and Trevan (51) have shown that the mesencephalon

plays an important part. According to Trevan, transection of the mesencephalon causes no disturbance of respiration until the level of the inferior colliculus of the corpora quadrigemina is reached. After a preliminary period of apnea respiration starts again at a slower pace somewhat as after double vagotomy. That the effect is not due to the cutting off of impulses from the vagus is shown by the fact that section of both vagi after removal of the inferior colliculi produces a further prolongation of respiration and slowing of the rate. The authors mentioned above are inclined to locate an accessory respiratory center in the inferior colliculus. Their evidence, however, indicates nothing more than that impulses which normally enter into the control of respiration pass through this level of the nervous system.

It is possible that Coombs and Pike (52) have hit upon the correct conception of the part played by the corpora quadrigemina in respiration. They have shown that the results of combined section of the vagus and dorsal roots are similar to those produced by section of the vagi plus transection of the brain stem below the corpora quadrigemina. These authors conclude that the afferent impulses from the intercostal muscles must go as far up as the mesencephalon from which they are directed backward to the respiratory center: and Graham Brown (53) has presented evidence indicating that in this downward part of their course they follow the tectobulbar tract.

While the inferior colliculus may be a necessary way station on the afferent path from the musculature of the chest wall to the respiratory center, the medulla oblongata is in itself sufficient for the establishment of the necessary connections between the afferent fibers of the vagus and the respiratory center. Furthermore it is not necessary for the majority of the somatic afferent impulses, which are capable of altering the respiratory rhythm, to reach the corpora quadrigemina before they become effective. Stewart and Pike (45) have demonstrated that all of the characteristic reflex respiratory effects of stimulation of the brachial nerves can be obtained through the bulbar center after anatomical separation from the higher centers. And Bechterew (43) states that stimulation of the trigeminal nerve causes active inspiration in an animal in which the brain stem has been divided below the level of the inferior colliculus.

Respiratory reflexes from various afferent nerves. A great deal of work has been done upon the changes in the respiratory rhythm that may be produced by afferent impulses traveling along the vagus, superior laryngeal, inferior laryngeal, trigeminal, acoustic, phrenic, sciatic, splanchnic

and other sensory nerves. The literature on this subject is voluminous and has been well summarized by v. Bechterew (43) and Sjöblonn (54). While it is clear that the respiratory center has connections with all of the afferent, cranial and spinal nerves, and the response may vary somewhat with the nerve stimulated, the effect of stimulation of a given nerve is not always the same. The rate and the amplitude may be increased or decreased. Either the inspiration or the expiration may be chiefly affected; or the respiratory movements may be inhibited in the expiratory or the inspiratory position. It is not always clear what determines the character of the individual response. The strength of the stimulus, the kind of anesthetic, and the particular nerve stimulated are important factors in determining what the effect will be. It would be useless at the present time to attempt an explanation of these variations.

It is possible that light might be thrown on the causes of these variations if carefully measured stimuli were applied successively to a large number of sensory nerves under rigidly controlled conditions. A start in this direction has been made by Gruber (55). The weakest effective electrical stimulation, measured in terms of Martin units, when applied to the vagus and the superior laryngeal nerve of the cat caused decreased inspiration with normal expiration; a somewhat stronger stimulus caused increased inspiration with decreased expiration; still stronger, respiratory inhibition in inspiration; and stronger yet cessation of respiration in expiration. It is obvious that these results may have a bearing on the question of the existence of two kinds of afferent respiratory fibers, but Gruber does not attempt any such interpretation of his results.

Afferent impulses from the lungs and chest wall. The vagus supplies afferent fibers to the larynx, trachea and lungs and these exert a dominant influence over the respiratory center. It is generally assumed that the afferent fibers of the vagus which end in the lung are of two kinds, inspiratory and expiratory. According to the theory of Herring and Breuer these two kinds of fibers are stimulated alternately by the expansion and collapse of the lungs. Stimulation of the expiratory fibers by the expansion of the lungs works through the respiratory center to limit the extent of inspiration, and initiate expiration. On the other hand, collapse of the lungs by stimulating inspiratory fibers may cut short the expiration and start a new inspiration. Blocking of these afferent impulses from the lungs by double vagatomy causes the respiration to be deeper and slows the respiratory rhythm. The inspiratory fibers in the vagus are, however, not supposed to be operative in quiet breathing but to come into play only during forced expiration (56).

The existence of vagal inhibitory fibers, which are stimulated by the expansion of the lungs and which because they limit the extent of inspiration and initiate expiration are also designated as expiratory fibers, seems to be well established. The case is not so clear for the existence of vagal inspiratory fibers although the consensus of opinion is that such inspiratory fibers do exist in the vagus. The most important evidence in support of this view has been presented by Head (57), Schenck (56), Einthoven (58), Nikolaides (59) and Sjöblonn (54). Schenk produced collapse of the lungs by suction and then clamped off the tracheal cannula. In these experiments the respiratory movements had a more expiratory character when the vagi were interrupted than when they were intact. He concludes that there are inspiratory fibers in the vagus which however, are stimulated only when the lungs are collapsed to an unusual degree. Einthoven (58) cut the vagi and connected the distal part with a string galvanometer, which then showed an action current throughout each inspiration. The lungs were then collapsed by suction and the galvanometer registered another electrical variation of a different character, indicating the existence of a set of fibers stimulated by this excessive collapse of the lung.

According to Nikolaides (59) the vagus of the bird differs from that of the mammal in that it contains chiefly inspiratory fibers. Its stimulation always results in rapid and deep respiration. He thinks that the inspiratory fibers are rudimentary in the mammal and can scarcely play a rôle in normal respiration while these fibers predominate in the bird. Sjöblonn (54) records an extensive series of stimulations of the central ends of sensory nerves, such as the phrenic, intercostals, sciatic, splanchnic and vagus. His results have not the value which they would have if they had been carried out with carefully measured stimuli. He found that the fibers in the vagus which inhibit inspiration are more easily excited than those which inhibit expiration. For this reason weak stimuli cause inhibition in inspiration and strong stimuli cause inhibition in expiration. But the results which Gruber (55) obtained with more carefully graded stimuli and which have been summarized on a preceding page are not susceptible of so simple an interpretation.

Two objections can be made to most of the evidence offered in support of the existence of inspiratory vagal fibers. Aspiration of air from the lungs has usually been employed to produce the excessive collapse of the lung necessary to stimulate these fibers. This produces a totally unnatural condition and necessarily results in temporary pulmonary congestion. And in the second place the investigators have not taken into

consideration the existence of afferent paths from the lungs and chest wall through the spinal cord to the respiratory center.

Barry (60) has made some very important contributions to this subject. He tested in rabbits and cats the effect of blocking the trachea at the end of an expiration or at the end of an inspiration, thus holding the lung in a condition of collapse or expansion. Blocking of the trachea at the end of inspiration causes inhibition of respiration and relaxation of respiratory muscles; but this result does not occur if the vagi have been previously divided. This confirms the existence in the vagus of expiratory (inspiration-inhibiting) fibers. Occlusion of the trachea at the end of expiration leads at once to a series of deep inspiratory efforts. The collapsed condition of the lung and chest wall therefore stimulates inspiratory fibers. But Barry says that the fibers in question do not run in the vagus because that nerve can be divided without diminishing the inspiratory reflex. On the other hand, this reflex was diminished by excision of the stellate ganglion and obliterated by section of the spinal cord. From these experiments Barry concludes that during ordinary breathing inspiratory impulses pass to the respiratory center by way of the spinal cord. These arise in the thoracic wall and travel by somatic nerves. There probably are also inspiratory impulses of pulmonary origin passing by way of the stellate ganglion, white rami and spinal cord. Afferent impressions of pulmonary origin conveyed by the vagus are chiefly inhibitory.

Gault and Scott (61) have shown by tracings taken from the cat's diaphragm that the slow respiration with prolonged expiration, characteristic of the vagotomised animal, gives place after section of the spinal cord in the low cervical region to a type of respiration in which both phases are prolonged. In a normal animal section of the cord, leaving the vagi intact, produces a respiration with prolonged expiratory phase. These results give support to Barry's contention that afferent inspiratory impulses are carried through the spinal nerves and spinal cord to the respiratory center.

Möllgaard (62) has demonstrated that afferent fibers reach the lungs by way of the sympathetic nervous system from the second and third spinal nerves. He also studied the chromatolysis in the sensory ganglia of the vagus resulting from excision of the lung and showed that the sensory vagal fibers which end in the lung have their cells of origin in the nodose ganglion and are to some small extent derived from the vagus of the opposite side.

Roger (63) stimulated the nerve endings in the bronchi and lungs of the rabbit by blowing an irritating gas through a tracheal cannula. Such irritation of the deeper respiratory passages regularly caused according to Roger a deep, prolonged and spasmodic inspiration followed by a short period of apnea and then rapid respiration. The afferent path for this reflex is through the sympathetic system and spinal cord since the reflex is not affected by double vagotomy. Craigie (64) has confirmed Roger's results on dogs with the exception that the first effect is a deep and prolonged expiration. The suspicion arises that Roger wrongly interpreted the upstroke of the recording lever from the manometer as indicating an inspiration. Mayer, Magne and Plantefol (65) by a somewhat similar technique obtained a sharp expiration followed by several jerky respirations and then polypnea. These reactions were stopped by section of the vagi or prevented entirely if these nerves were cut before vapor was applied.

The importance of the dorsal roots of the spinal nerves as paths for the afferent impulses involved in the respiratory reflexes, is obvious from the results of Barry, Gault and Scott, Möllgaard and Roger. Additional evidence along this line has been furnished by Coombs (66) and Coombs and Pike (52), who found that section of the thoracic and cervical dorsal roots results in a diminution or cessation of costal respiration without marked change in the respiratory rhythm.

Apnea. Apnea has been divided into three classes: true, vagal and false apnea. The term vagal apnea is applied by some authors to the arrest of respiration which results from stimulation of the pulmonary endings of the vagus by distention of the lungs, and the term false apnea to a similar arrest produced by the stimulation of other sensory nerves. It is doubtful if such reflex inhibition should be designated as apnea, since according to most observers the inhibition does not outlast the stimulus. In recent years the conception advocated by Haldane has become dominant that true apnea is of chemical origin. It is true that Githens and Meltzer (67) have seen prolonged and complete apnea follow short distention of the lungs with air containing 5 per cent of CO_2, and that Foa (68) has also made observations which seemed to him to indicate that the vagus played a part in the production of true apnea. Most recent investigators, however, find that the occurrence of apnea is entirely dependent upon the chemical stimulation of the respiratory center and that, while distention of the lungs brings about a reflex inhibition of respiration, this inhibition does not last beyond the time of distention if sufficient CO_2 is added to the air to maintain the alveolar content of CO_2 unchanged (69), (70), (71), (72), (73).

Leroy (74) has repeated Fredericq's cross circulation experiment, the result of which had been called in question by Foa (68), and confirmed Fredericq's results. In this experiment the central end of the carotid of one rabbit is united with the peripheral end of the carotid of another rabbit and vice versa. All other head arteries are tied. Changes in the blood gasses of A alter the respiratory rhythm of B. Very strong ventilation of the lungs of A, produces apnea in B increasing the alveolar content of CO^2 in B's lung and thus producing dyspnea in A. Since the series of responses is not affected by double vagotomy it is in no way dependent upon a reflex through the vagus. The question thus seemed to have been settled in favor of the Haldane school, but has been reopened by Meek (75) who ranges himself on the side of the minority.

Reflexes from the upper respiratory passages. Stimulation of the mucous membrane of the pharynx, larynx and trachea or of the nerves which supply this territory, namely, the glossopharyngeal, superior laryngeal and recurrent nerves leads to inhibition of respiration in the expiratory position. During the act of swallowing respiration is inhibited by afferent impulses which arise in the pharyngeal mucosa and travel along the glossopharyngeal nerve (250). Irritation of the sensory endings of the trigeminal nerve in the nasal mucous membrane leads to the same results (65), and in addition it causes marked cardiac and vasomotor reflexes (63). Pressure on the bulbus oculi likewise produces through the trigeminal nerve an alteration in the rate and amplitude of respiration associated with oculo-cardiac and oculo-vasomotor reflexes (114).

If water is poured over the muzzle of a tracheotomized animal, respiration ceases in the expiratory phase. This can be seen to good advantage in water fowl. Submergence of a duck's head under water produces instantly reflex inhibition of respiration. Since submergence of the entire head is required the receptors involved must be those which supply the mucous membrane and skin of the head, chiefly the trigeminal and glossopharyngeal nerves (76), (77). (See also Vincent and Cameron (78).) It is obvious that these reflexes have for their object the exclusion of noxious gasses and other injurious substances from the lungs. This protective action is made more evident by the fact that together with the cessation of respiration the glottis is reflexly closed and the bronchial musculature contracted.

It has been demonstrated that stimulation of the trigeminal nerve endings in the mucous membrane of the nose will cause a reflex contraction of the bronchial musculature (79). Dixon and Brodie (80) could pro-

duce no effect on the bronchial musculature by stimulation of the central end of the vagus or the sciatic nerve. But they found that electrical, chemical or mechanical stimulation of the nasal mucous membrane usually results in some degree of bronchial constriction which as a rule comes on gradually and is very persistent.

Exaggerated contraction of the bronchial musculature brings on a condition of labored breathing known as asthma. The prompt and permanent relief, which sometimes follows removal of nasal irritation, suggests that in these cases asthma is caused by bronchial spasm reflexly excited from the nose (81), (82), (83), (84), (85), (86). This form of asthma falls in the class of nasal reflex neuroses. Under this heading are included a great variety of conditions supposed to be caused by irritation of the sensitive mucosa of the nose and accessory sinuses (87), (88), (89).

This is perhaps the place to mention the interesting results of Carlson and Luckhardt (1) on the amphibian and reptilian lung. In the frog and turtle there are muscle fibers in the lung which, when they contract, cause the lung to shrink. The degree of contraction of this lung musculature can be affected reflexly through central stimulation of the vagi or of cutaneous nerves.

CARDIAC REFLEXES. While the genesis of the heart beat may now be definitely traced to the sino-auricular node, which is the "pacemaker" for the mammalian as well as the lower vertebrate heart (92), yet the cardiac rhythm is under the influence of the central nervous system through inhibitory fibers in the vagus and accelerator fibers in the sympathetic nerves, and the pulse rate may be altered reflexly by afferent impulses from many sources.

An increase in blood pressure causes a slowing of the rate of the heart beat, which is at least in part of reflex origin. The effect of the pressure on the heart is but a minor factor. Herlitzka (93), who worked with the isolated dog's heart fed with Locke's solution found that the cardiac rate increased with the pressure but that the change did not occur for some time and was apparently due to better nutrition of the heart. Eyster and Hooker (94), (95) have reviewed the literature on this subject and conclude that the balance of evidence supports the view that in the isolated heart no changes in rate occur as a result of changes in blood pressure, that cannot be referred to changes in nutritive conditions. These authors conclude that the slowing of the heart from increased arterial pressure is due to two factors which normally act together: *a*, a direct effect of the increased blood pressure upon the

cardio-inhibitory center; and *b*, a stimulation of the cardio-inhibitory center through afferent nerves, resulting in a reflex slowing of the heart. They believe that the afferent fibers concerned in this reflex come, at least in large part, from the thoracic aorta, since increased pressure acting only on this part of the aorta caused slowing of the pulse while increased intraventricular pressure was without effect. Since the cardio-inhibitory reflex persists after section of the accelerator and depressor nerves, the afferent as well as the efferent path must be in the vagus. Their experiments do not prove that there are no afferent fibers for this reflex in the depressor or accelerator nerves but do show that they are not exclusively found in these nerves. It has been shown by von Brücke (96) that stimulation of the central end of the depressor nerve, which is now known to be the afferent nerve of the aorta (97), causes a slowing of the heart amounting to 25 per cent. On the other hand Kochmann (98) thinks that the sensory endings involved in the cardio-inhibitory reflex are in the heart. Stimulation of the central end of the vagus causes slowing of the heart rate; and Brodie and Russell (99) have shown that in producing this reflex the pulmonary branches are most effective, the cardiac branches much less effective and those below the pulmonary still less so.

This reflex has been regarded as due to a stimulation of the cardio-inhibitory center but the results of von Brücke (96) indicate that there is at the same time an inhibition of the tonic action of the accelerators. Stimulation of the central end of the depressor nerve in the rabbit gave a reduction in the heart's rate of 25 per cent before and 8.5 per cent after double vagotomy. Extirpation of the stellate and inferior cervical ganglia along with double vagotomy completely eliminated the reflex slowing of the heart from depressor stimulation. On the other hand Bainbridge (100) was unable to demonstrate any slowing of the heart by central vagus stimulation after double vagotomy in dogs and concludes that such stimulation does not decrease the tone of the accelerator centers.

It is well known that stimulation of the central end of the sciatic and many other sensory nerves reflexly quickens the heart. Until recently it was believed that this was brought about entirely through a diminution of the tone of the vagus. Hooker (101) has shown, however, that if both vagi are cut and a stimulus is applied to the peripheral end of one of them, just sufficient to keep the heart beating at the rate previously observed in the intact animal, it is possible to obtain a reflex acceleration of the heart from stimulation of the central end of the vagus, splanchnic

sciatic and saphenous nerves. Since in these experiments the vagi were cut, the response must have been due to a stimulation of the accelerator centers. Bainbridge (100) has obtained similar results from sciatic stimulation in dogs in which after double vagotomy the cardiac rate was slowed by peripheral vagus stimulation or by pilocarpin. He concludes that although reflex cardiac acceleration is mainly due to a decrease of vagus tone there also occurs a stimulation of the accelerator centers. The work of Petzetakis and Dastre (103) would seem to indicate that the reflex arc for cardiac acceleration from stimulation of the sciatic nerve is complete below the medulla oblongata, since the response is not abolished by section of the cervical portion of the spinal cord.

It has been shown by Carlson (102) that during periods of strong hunger contractions the rate of the heart is increased. Dmitrenko (166) found that dilatation of the stomach by inflating a balloon within its lumen causes a quickening of the pulse. Most of the centripetal fibers for this reflex are in the splanchnic nerve but a few also occur in the vagus and the response is due to the excitation of the accelerator mechanism not to the inhibition of the cardiac inhibitory center.

The quickening of the pulse which occurs during exercise is in large part brought about through depression of the cardio-inhibitory center but it is not known whether this occurs as a reflex from the sensory terminals in the active muscle or is caused by an irradiation of impulses from the pyramidal tract to the cardio-inhibitory center. Since this response has not been clearly shown to be a reflex, it falls outside the scope of this paper. The related literature has been discussed and the problem thoroughly investigated by Gasser and Meek (104).

Afferent fibers from the respiratory tract seem to have particularly intimate connections with the cardio-inhibitory center. Central stimulation of the pulmonary branches of the vagus is more effective than that of the cardiac branches in slowing the heart (99). In the frog, irritation of the lungs causes cardiac inhibition while in the turtle cardiac acceleration is obtained from the pulmonary branches of the vagi (105). An irritant vapor blown directly into the bronchi through a tracheal cannula causes reflex cardiac inhibition (63). Collapse of the lung due to opening of the chest causes a reflex slowing of the heart which does not occur if the vagi are cut (106). The question whether the afferent path for this reflex is in the vagus or sympathetic nerves cannot be answered by section of the vagi since these nerves also contain the efferent limb of the arc. Similar cardio-inhibitory responses can be obtained from the stimulation of the trigeminal nerve endings in the nasal mucosa and of

the vagus endings in the larynx (99), (63). Weil and Philippe (107) have studied this naso-cardiac reflex in some detail and find that mechanical as well as chemical irritation of the nasal mucosa may cause either a slowing or quickening of the pulse, the afferent path for this reflex being in the trigeminal nerve. It closely resembles the oculocardiac reflex.

This relatively unimportant oculocardiac reflex has engaged the attention of a great number of investigators since it was first described in 1908 by Aschner (110) and Dagnini (111). Pressure on the eyeball causes a slowing of the pulse. The afferent path for the reflex is in the trigeminal nerve. A few of the more important articles on this subject are included in the bibliography (112), (113). (114), (115), (116), (117), (118), (119).

VASOMOTOR REFLEXES. The arterial blood pressure is maintained by the action of the heart working against a peripheral resistance that increases or decreases with changes in the caliber of the blood vessels. Constriction of the arterioles causes a rise in blood pressure, and a blanching of, and decreased blood flow through the parts of the body affected by the constriction. Dilation of the arterioles and capillaries causes a fall of arterial pressure, and a flushing of, and increased blood flow through the parts affected. The caliber of the arteries and probably also that of the capillaries (120) and at least some of the veins (121) is under the control of the nervous system. The efferent fibers which bring about contraction of the blood vessels are known as vasoconstrictor and those which cause dilatation as vasodilator fibers.

While mental and emotional states often find expression in blanching or flushing of the skin and in changes in blood pressure, vasomotor control is for the most part reflex in character; and a reflex involves afferent as well as efferent conductors and a center in the segmental portion of the nervous system. Afferent fibers whose stimulation causes vasoconstriction and a rise of blood pressure have been designated as pressor fibers, and those which cause a fall in blood pressure as depressor fibers.

Vasomotor centers. Many of the vasodilator responses are axon-reflexes, peripheral in origin and local in character (122); but all other vasomotor responses are mediated through the central nervous system and are under the control of a vasomotor center located in the medulla oblongata at about the level of the motor nucleus of the facial nerve. This is primarily a vasoconstrictor center serving both as a center for pressor reflexes and through its tonic activity for the maintenance of the

vascular tone. The tonic activity of this center is no doubt in part due to the continual play upon it of afferent pressor impulses; but it is also capable of responding to the carbon-dioxide concentration of the blood and to the amount of blood supplied to the medulla (123). Porter (124), (125) presents what does not seem to be altogether satisfactory evidence that the vasomotor center consists of two distinct parts, a vasotonic and a vasoreflex center. A more important question in view of the recent work on vasodilator reflexes is whether there is in addition to the vasoconstrictor center also a vasodilator center and what are the structural and functional interrelation of these two centers. It has been demonstrated that depressor stimulation causes not merely a depression of the tone of the vasoconstrictor center but also an active vasodilatation involving widely separated parts of the body such as the nasal mucous membrane, the tongue and the hind limbs even after the vasoconstrictor fibers to these parts have been divided (126), (127), (128). These so-called active vasodilator responses are not due to an inhibition of the vasoconstrictor center; and it is hard to see how they could be mediated through that center. In the absence of clear evidence for the existence of a coördinating center for these vasodilator responses it is possible to assume that the incoming vasodilator impulses play upon widely separated groups of neurons in the brain stem and spinal cord, through which the efferent vasodilator impulses are transmitted. But in view of the wide dissemination of the dilator impulses entering through the depressor nerve as demonstrated by Fofanow and Tschalussow (127), the hypothesis, advanced by Bayliss (129) and supported by the authors just mentioned, that there exists a special vasodilator center does not seem unreasonable. But Martin and Stiles (130), although they have presented evidence that the fall of blood pressure from depressor stimulation is due in part to a stimulation of the vasodilator mechanism, do not regard it as necessary to assume the existence of such a coördinating vasodilator center. The observations of Ranson and Billingsley (131), that there are in the floor of the fourth ventricle of the cat a pressor point in the fovea inferior, the stimulation of which causes a rise in blood pressure, and a depressor point in the area postrema, which when stimulated causes a fall, indicate that at each of these points some portion of the corresponding reflex arc is accessible to stimulation. They do not necessarily indicate the location at these points of separate vasoconstrictor and vasodilator centers.

Since the vasoconstrictor center exerts its influence through the spinal visceral efferent neurons it is possible that these neurons located in the

intermediolateral cell column may under certain conditions be accessible to influences other than those reaching it from the vasoconstrictor center. There is evidence that this actually occurs. Some considerable time after transection of the lower cervical spinal cord of the dog, Sherrington (132) obtained a clear cut pressor response from sciatic stimulation. Since this reflex cannot be obtained immediately after transection, and since division of the afferent spinal pressor pathway in the upper cervical region without the production of spinal shock entirely eliminates the pressor response (162), we may conclude that these so-called spinal vasomotor centers are not under ordinary conditions accessible to the incoming pressor impulses, but rather that these must first ascend to the bulbar vasomotor center before they can become operative. That the inaccessibility of the spinal vasomotor centers to afferent pressor impulses is not due to spinal shock caused by the stimulation of inhibitory fibers during the transection of the cord is also demonstrated by the fact that paralysis of the medulla by cocain or by cold abolishes the pressor responses although neither of these means would stimulate any inhibitory fibers (133), (134). But according to Japelli (135) the spinal vasomotor centers are rendered accessible to pressor impulses from the sciatic shortly after transection of the cervical spinal cord if the animal is partially asphixiated.

Vasomotor reflexes from somatic nerves. Stimulation of the central end of a sensory nerve like the sciatic may under appropriate conditions result in either a rise or a fall in blood pressure. It has been known for many years that strong stimulation of any general somatic sensory nerve causes a vasoconstrictor reflex. Certain nerves, such as those which supply the muscles, have been thought to be more liable to cause a vasodilatation than others; but recent work has shown that there is no essential difference in the reaction to be obtained from the various somatic nerves (136), (137), (138). Those who have recently worked with the vasomotor reflexes have for the most part devoted their attention to the depressor responses. Busquet (139), (140) secured tracings from the dog's femoral artery and vein and found that jarring the table or pinching the foot caused a drop in arterial and a rise in venous pressure. The vasodilatation thus indicated is reflex since it is abolished by section of the sciatic nerve or of the spinal cord below the medulla.

Hunt (141) was the first investigator to study carefully the conditions under which afferent somatic nerves give depressor responses. He found that weak stimulation, or stimulation of a nerve previously cooled, or stimulation of a regenerating nerve would regularly elicit a fall in

blood pressure. Martin and Lacey (136) found that a reflex drop is the typical response to stimulation of the somatic afferent nerves when the stimulation is in the order of magnitude of the threshold for spinal reflexes of the skeletal muscles. This is from 20 to 200 times less than that required to induce the pressor response. Gruber (142) and Gruber and Kretschmer (143), working with cats anaesthetized with urethane, showed that the rate of stimulation was an important factor in the response. With weak faradic stimulus and four interruptions per second they obtained a drop in blood pressure in every case, and with strong stimuli and one interruption per second they obtained a drop in 93 per cent of the trials. Vincent and Cameron (137) were inclined to doubt the reflex character of the depressor response from somatic nerves since, because they did not pay sufficient attention to the rate of stimulation, they were unable to secure clear-cut results. But, taking advantage of Gruber's results on the rate of stimulation, Vincent and Ogata (138) went again over the same ground and were able to demonstrate a definite somatic depressor reflex. The depressor response from somatic nerves, like that from the vagus and depressor nerves, seems to be due in part at least to an active vasodilatation. Martin and Mendenhall (128) state that weak stimuli excite the vasodilator mechanism to activity. The result is a general drop in blood pressure, with active dilatation in such organs as are provided with vasodilator nerves. But this phase of the subject can best be discussed in connection with the vagus and depressor nerves.

Pressor and depressor reflexes from the same nerve may be explained on either of two hypotheses. There may be two kinds of afferent vasomotor fibers in the nerve. Or there may be a single type and each such fiber may make such connections in the central nervous system that the impulses which it carries can under appropriate conditions call forth one or the other vasomotor response. According to current physiological doctrine there are at least two such types; and they are designated as pressor and depressor fibers respectively. Let us see what the evidence is on this point. Stimulation of the central end of a sensory nerve like the sciatic will cause a rise or a fall of blood pressure according to the conditions of stimulation. If weak, the stimulation tends to produce a drop; if strong a rise; if the nerve is cooled the same stimulus that before gave a rise now gives a fall; stimulation of a nerve in the early stages of regeneration will give a drop rather than a rise (141). It is also significant that a stimulus applied but a few times per second will give a fall while the same stimulus if rapidly repeated will cause a rise (142), (143)

(138). The generally accepted explanation of these facts is that put forward by Hunt (141), (144), namely, that the afferent vasomotor fibers are of two kinds: pressor fibers causing a rise and depressor fibers causing a drop in blood pressure. The latter are supposed to be more susceptible to weak stimulation and to stimuli which are repeated but a few times per second, more resistant to cooling and more rapidly reëstablished in regeneration.

According to the accurate quantitative studies of Martin and Lacey (136) the threshold for the pressor reflexes from somatic sensory nerves is from 20 to 200 times as great as that for depressor reflexes. They point out that the effect of the means used by Hunt to produce depressor reflexes (cooling of the nerve or the use of a regenerating nerve containing but a few fibers) would be to prevent massive stimulation from reaching the central nervous system. The great difference between the thresholds for pressor and depressor reflexes has been confirmed through further work by Martin and Stiles (130) and Martin and Mendenhall (128). Since however the depressor threshold is of the same order of magnitude as that for skeletal reflexes it is not to be regarded as excessively low. On the contrary, the pressor threshold is unusually high and far beyond that for other sensory fibers.

Ranson and Billingsley (145) thought it hard to believe that two nerve fibers could be so differently constituted that one should have a threshold from 20 to 200 times greater than the other and this argument has greater weight when it is considered that the one with the lower threshold agrees in this respect with the afferent fibers for the flexion reflex (146) and such preganglionic autonomic fibers as have been tested (147). In the response from a preganglionic autonomic fiber and in the flexion reflex at least one synapse is involved. Where no synapse is involved as in a nerve muscle preparation the threshold is but half as great (146). If the presence of a synapse in the path doubles the threshold for a response one can easily understand how the numerous synapses in the pressor path raise the threshold for the corresponding reflex to so great a height (see p. 498). Gruber's demonstration that the rate of stimulation of a sensory nerve is largely responsible for the type of vasomotor response obtained, that moderate stimuli if rapidly repeated may cause a rise and that strong stimuli if not repeated more than once a second may cause a drop has been advanced by Hunt (144) as tending to weaken the force of the argument just presented. But to the present writer Gruber's results seem rather to reinforce that argument since the summation which is obviously involved in those results is more the property of the synapse than of the nerve fiber.

It is possible to frame an alternative hypothesis which would obviate the difficulty but this can best be discussed in connection with the afferent pressor and depressor paths within the spinal cord.

On either hypothesis it is necessary to assume a balanced action between two antagonistic mechanisms, the depressor mechanism is brought into action alone by stimuli too weak or too slowly repeated to affect the pressor mechanism. But the latter is more powerful and when once brought into action it quickly overpowers its antagonist (128) (145).

Relation of sensory to afferent vasomotor fibers. The general somatic nerves convey in addition to deep sensibility also tactile, thermal and painful impulses. It is possible, indeed probable, that the afferent vasomotor impulses are not transmitted by a separate group of fibers but rather by one or more of the groups of fibers responsible for the several modalities of sensation. It is well known that exposure to cold causes blanching of the skin reflexly through the cold receptors and sensory fibers of the skin, and that warmth causes reflex flushing (148), (149), (150). Reflex vasoconstriction from chilling of the body surface is not confined to the skin but also involves the mucous membrane of the pharynx (151). To produce a generalized vasodilatation, the heat applied must not be of sufficient intensity to cause pain otherwise a vasoconstrictor reflex will result (150). Reflex vasodilatation from application of warm water to the skin and vasoconstriction from immersion in cold water has been amply demonstrated in man by clinical observation (152), (153), (154).

The alteration in the character of the response from vasodilatation to vasoconstriction, as the warm application becomes painfully hot, indicates that the pain receptors and pain fibers receive and convey vasoconstrictor impulses. Stimulation of mixed nerve trunks can of course give no information on this subject. But even in anaesthetized animals it is possible to cause well-marked vasoconstrictor reflexes by stimulation of the pain receptors. This can easily be demonstrated by rapidly painting an area of skin with nitric acid in a cat whose blood pressure is being recorded. More conclusive evidence is given by an unpublished observation of Miss Wilson (155) that electrical stimulation of the cornea, which contains only pain receptors, causes a well-marked pressor response.

It is clear that stimulation of the heat receptors causes vasodilatation, and of the cold and pain receptors vasoconstriction, but the case is not so clear for tactile receptors. The classical observation in this connection is that of Grützner and Heidenhain (156). These investigators

found that gently stroking or blowing on the hair of curarized but unanesthetized rabbits caused vasoconstriction; and Langley (157) was able to confirm these results in decerebrate rabbits. But Martin, Franklin and Hield (150) found that, while vasoconstriction could be produced in one ear by blowing on the other ear in the normal unanesthetized rabbit, only a suggestion of such a response could be obtained after decerebration. The same was true for the response produced by shrill whistling. They conclude that mild tactile and auditory stimulation is productive of vasoconstriction only when it operates to bring about psychic excitation, which latter is the immediate cause of the vasomotor activity. But the responses to thermal stimuli are of reflex origin and persist after decerebration. The reflex character of the thermal vasomotor reactions has also been demonstrated by Winkler (158). These facts agree with the results of Ranson and Billingsley (159) who worked on the dorsal roots of the cat and found that the pressor reflex was obliterated by section of the lateral division of the root, which for many reasons is believed to contain the pain and temperature fibers; while this reflex was not affected by section of the medial division, which probably contains the tactile fibers (160). The relation of the afferent vasomotor fibers to the several varieties of sensory fibers deserves further investigation.

Afferent vasomotor paths within the spinal cord. Ranson, von Hess, and Billingsley (131), (159), (161), (162, (163) have investigated in cats the afferent paths within the spinal cord for vasomotor reflexes. They found that the pressor fibers enter the cord through the lateral division of the dorsal root. This division of the root is composed chiefly of unmyelinated fibers which enter the tract of Lissauer, while the medial division is formed of myelinated fibers that enter the posterior funiculus. In the first sacral dorsal root these divisions are so placed that either may be cut without appreciable damage to the other. Section of the medial division had no effect on the pressor reflex, while section of the lateral division obliterated that reflex. Unfortunately no tests of the depressor response were made on these roots. In keeping with these observations on the dorsal roots is the easily demonstrated fact that section of the posterior funiculus, which contains the ascending branches of the fibers of the medial divisions of the dorsal roots, is without effect on the vasomotor reflexes. On the other hand bilateral destruction of the apex of the posterior horn (substantia gelatinosa Rolandi) and the overlying tract of Lissauer obliterated the pressor reflex from central stimulation of the sciatic nerve. Such a lesion does not, however,

interfere with the depressor reflex from that nerve. On the other hand, bilateral section of the lateral funiculi eliminates the depressor without decreasing the pressor response. These experiments demonstrate that the two types of afferent vasomotor impulses travel separate paths in the cord. The pressor path is located in the apex of the posterior horn and the tract of Lissauer, while the depressor path is in the lateral funiculus. Unilateral lesions demonstrate that the afferent vasomotor impulses, induced by the stimulation of a nerve or nerves on one side of the body, travel up both sides of the cord. But, while the conduction of depressor impulses is somewhat better on the contralateral side, the pressor impulses seem to ascend about equally well on both sides. The location of the depressor path in the lateral funiculus might suggest that it was identical with the spinothalamic tract; but the fact that decerebration does not obliterate either the depressor or the pressor reflex shows that both of these arcs are complete below the thalamus.

It is well known that the trigeminal nerve gives, when stimulated, the same vasomotor response as a spinal nerve. Now it is also known from clinical evidence that pain and temperature sensations for the face are mediated through the spinal tract of the trigeminal nerve which descends through the medulla to become continuous with the tract of Lissauer in the spinal cord. Lesions, destroying the spinal tract of the fifth nerve, cause loss of pain and temperature sensation on the corresponding side of the face without impairment of touch (Winkler (164) and many others). Here is offered again an opportunity to compare the course of the pressor impulses with that of the afferent impulses underlying pain and temperature sensations. This test has recently been applied by Miss Wilson (155) on the cat; and she has demonstrated that the pressor impulses also descend through the spinal tract of the fifth nerve. Section of this tract in the upper part of the medulla obliterates the pressor response from the corresponding trigeminal nerve although the connection of that nerve with its main sensory nucleus is not interrupted and although tactile sensibility has not been impaired. The spinal tract of the fifth nerve and its nucleus forms with the tract of Lissauer and the substantia gelatinosa Rolandi a continuous column; and so closely does the cranial part of this column resemble the spinal part that it is not possible to tell where one ends and the other begins. We now know that this column receives the pressor impulses from the trigeminal as well as from the spinal nerves.

Since the fibers in the tract of Lissauer and the apex of the posterior horn are all short, the pressor path, which as we have seen runs through

this part of the cord, must be composed of chains of short neurons with many synapses. On the other hand the depressor path in the lateral funiculus is composed of long fibers. It seems clear that the different anatomical characteristics of these two spinal paths are sufficient to account for the two types of vasomotor reflexes without the necessity of assuming the existence of two kinds of afferent vasomotor nerve fibers. The facts which originally lead to this assumption are more easily explained by the characteristics of these two spinal paths. Very strong stimuli or rapidly repeated stimuli of moderate strength are well suited to break down the high synaptic resistance in the pressor path and for this reason are able to cause a rise in blood pressure. Weaker stimuli, that is such as are of the same order of magnitude as those required to produce skeletal reflexes, are able to make their way to the vasomotor center through long fibers of the depressor path in the lateral funiculus. It is also in keeping with this theory that the depressor should reach the vasomotor center before the pressor impulses and that the latent period for reflex vasodilatation should be less than for vasoconstriction (128). This longer latent period of the vasoconstrictor response from strong stimulation will be hard to explain on the basis of two kinds of afferent fibers.

The demonstration of these two afferent vasomotor paths in the spinal cord does not of course exclude the possibility that there may also be separate pressor and depressor fibers in the peripheal nerves. That there is a certain amount of truth in this assumption is shown by the differences in the response to stimulation of the heat and cold nerve endings in the skin. But many of the facts which could previously be explained only on the basis of this assumption are now more readily accounted for in another manner.

Afferent vasomotor paths from the viscera. Because of the depressor responses obtained from the glossopharyngeal, vagus and splanchnic nerves as well as from the depressor nerve, one might be justified in assuming that afferent impulses arising in the viscera are much more likely to cause a drop in blood pressure than those coming through somatic nerves. With this in mind Ranson and Billingsley (163) suggested that this might be due to the fundamentally different central connections of visceral and somatic afferent fibers. The one group makes connection with the visceral column of afferent nuclei and the other with the somatic column; and the secondary afferent paths from these two nuclear columns are not the same.

But the problem is much more complicated than it appears at first

glance. Vasoconstrictor responses are readily obtained from certain visceral nerves. Miller (165) found that stimulation of the central end of the gastric vagus in anaesthetized rabbits caused a rise in blood pressure; but in cats the response was complicated by the vomiting that the stimulation induced. Dmitrenko (166) found that inflation of a rubber balloon in a dog's stomach was followed by a reflex rise in blood pressure along with acceleration and deepening of the respiration. The same reflex was also produced by stimulation of the peritoneal covering of the stomach and by contraction of the stomach however produced. Stimulation of the mucosa was without effect. He argues that vasoconstrictor impulses may be initiated in the muscular and serous coats of the stomach but not in the mucosa. Carlson (167) has shown that rhythmic changes in circulation run parallel to the hunger contractions of the empty stomach. The plethysmograph showed an increase in the volume of the arm (vasodilatation) pari passu with increasing tonus of the stomach. Since this occurred when the subject was asleep the inference is that the reaction is reflex in character. When hot or cold water is introduced into the stomach in quantities of 50 to 100 cc. at a time there nearly always results a vasoconstriction as registered by the plethysomgraph on the arm. But since this response can not be obtained when the subject is asleep, Carlson thinks it is due mainly to the effect of conscious processes on the vasomotor center.

It has been thought by some that vasodilatation resulting from handling the intestines was a factor in the production of shock in laporotomies; but Seelig and Lyon (168) and Muns (169) have shown that manipulation and chilling of the intestines leads to vasoconstriction of the vessels of the leg.

Even the depressor nerve of the rabbit has a connection with the vasoconstrictor center as has been demonstrated by Stewart and Pike (45). They have shown that at a certain stage in resuscitation after cerebral anemia, only pressor responses may be obtained by stimulating the depressor. Under the same conditions the response from central stimulation of the cat's vagus, which normally is a drop, becomes a rise in pressure. Fafanow and Tschalussow (127) state that there is no ground for regarding the depressor nerve as composed exclusively of depressor fibers. That nerve is a branch which in certain animals is given off from the vagus and like the vagus it contains both pressor and depressor fibers.

Stimulation of the central end of the vagus causes the opposite response in the dog from that which it does in the cat. In the dog the usual response is a rise in blood pressure; in the cat it is a fall (170). This is

particularly interesting in connection with the facts regarding the vasomotor reactions obtainable from the central end of the splanchnic in these animals.

In dogs the vasomotor reflex from the splanchnic nerve closely resembles that from the depressor nerve in the rabbit. Auer and Meltzer (171) did not obtain a rise from central stimulation of the dog's splanchnic in a single case but rather drops in blood pressure amounting in some cases to as much as 60 mm. Burton-Opitz (172), (173), working with dogs anesthetized with ether, found that stimulation of the central end of the thoracic sympathetic caused a marked fall in blood pressure unless the stimulus was too strong. He regards the splanchnic nerve as the depressor nerve for the abdominal viscera. In the cat, on the other hand, stimulation of the central end of the splanchnic nerve causes a rise in blood pressure comparable to that obtained from the sciatic. This fact was noted by Auer and Meltzer. Davis (174) has found that any stimulus strong enough to produce a reflex vascular response through the cat's splanchnic nerve always causes a rise. He has not, however, checked his results by the use of stimuli repeated but a few times per second, and it is possible that in this way depressor responses might be obtained from the splanchnic nerve of the cat.

In the dog, then, stimulation of the central end of the vagus ordinarily gives a rise in blood pressure while a fall is obtained from the central end of the splanchnic. In the cat, on the other hand, a fall is the usual response obtained from the vagus, while the splanchnic gives a rise. The interpretation of these facts must await further investigation.

The depressor will under almost all conditions of stimulation yield a depressor reflex. In the rabbit and some other animals it appears as a separate strand accompanying the vagus. The fibers of this nerve terminate in the wall of the aorta (97) where they are stimulated by an increase in blood pressure. Their function is to serve as an automatic check against excessive arterial tension by reflexly slowing the heart (96) and relaxing the arteries. This vascular reaction is not confined to the splanchnic area alone but affects other parts of the body as well (175), (176), (127). Fafanow and Tschalussow state that stimulation of the depressor causes a dilation of the vessels in the entire body. Dilatation of the vessels of the kidney as well as those of the spleen results from depressor stimulation as Sollmann and Pilcher (177) demonstrated by the perfusion method.

Sollmann and Brown (179) have described what appears to be a new depressor reflex. After division of the common carotid artery traction

on its cephalic end causes a fall in blood pressure, the origin of which they traced to the nerve plexus which surrounds the beginning of the internal carotid. The reaction was not affected by section of the vagus or of the spinal nerves. There is a small branch from the glossopharyngeal nerve to the carotid body and internal carotid artery (180), (182). The existence of this branch in the cat, dog and man has been confirmed by Billingsley and Wilson (183), and its relations are such that it would have been put under tension in the experiments just described. In view of the ease with which depressor reactions can be obtained from the glossopharyngeal nerve it may be that this branch was responsible for the carotid reflex.

With regard to the intramedullary course of the afferent impulses from the viscera very little is known. From anatomical evidence it is known that the visceral afferent fibers of the glossopharyngeal and vagus nerves run downward in the medulla within the tractus solitarius and terminate in the nucleus associated with that tract. From this visceral receptive nucleus the afferent vasomotor impulses carried by these nerves must make their way directly or indirectly to the vasomotor centers. Even less is known concerning the course of visceral afferent impulses within the spinal cord. Davis (174) has recently demonstrated that the pressor impulses, caused by stimulation of the central end of the splanchnic nerve in the cat, do not follow the same path upward in the spinal cord as do the pressor impulses generated by stimulation of the somatic nerves. Division of the posterior funiculus and the posterior gray columns of the cord at the level of the first thoracic segment does not affect the pressor reflex from the splanchnic, although it does obliterate this reaction from the sciatic nerve. Davis thus confirms the observation of Ranson, von Hess and Billingsley (161), (162) that the afferent pressor path from the somatic nerves is in the tract of Lissauer and apex of the posterior gray column, and at the same time demonstrates that this path does not serve for the conduction of pressor impulses from the viscera. Transection of the cord at the level of the first thoracic segment does obliterate the response from the splanchnic, indicating that it is not a purely spinal reflex. The impulses concerned must ascend to the medulla in either the lateral or the ventral funiculus.

The relation of the depressor paths to the vasomotor centers. It has quite generally been assumed that the depressor responses are due to an inhibition of the vasoconstrictor center but as we shall see this represents only half the truth. The drop in blood pressure has in reality a double origin without taking into consideration the factor of cardiac inhibition.

Bayliss (129) has clearly demonstrated the double nature of the response to central vagus excitation in the vessels of the cat's salivary gland. An increased rate of flow through the gland was obtained even after elimination of the vasoconstrictor fibers by section of the cervical sympathetic trunk, indicating that there is a true reflex vasodilatation and not merely an inhibition of constrictor tone. Since, however, central vagus excitation caused an increased flow of blood through the gland when the cervical sympathetic was intact and the dilator nerve, the chorda tympani, cut, it is evident that a part of the result is due to an inhibition of vasoconstrictor tone. Fofanow (184), Tschalussow (185), (186) and Fofanow and Tschalussow (127) have presented evidence that an active vasodilatation is induced by depressor stimulation. In their joint papers published in 1913 these authors divide those who have investigated the action of the depressor and vago-depressor nerves into three groups. The majority, they say, have interpreted the results as due to an inhibition of the vasoconstrictor center, while the second group, who attribute the action to a stimulation of a vasodilator center, includes only one recent investigator, Francois-Frank (187). The third group, including Bayliss and themselves, consists of investigators who regard the effect as due both to a stimulation of the dilator center and an inhibition of the constrictor center.

The experiments of Fofanow and Tschalussow (127) are more than usually instructive. They determined the change in volume of the tongue and hind limb, due to reflex vasodilatation in dogs and cats in which the vasoconstrictors to these parts had been eliminated. Under these conditions they obtained clear cut vasodilator reflexes in both the tongue and the hind limb from the stimulation of the vago-depressor nerve. They conclude that depressor stimulation causes an excitation of the vasodilator center as well as an inhibition of the constrictor center.

Similar results have been obtained by Tschalussow (186) on the nose. He was able, after elimination of the constrictor fibers by division of both sympathetic trunks in the neck, to obtain reflexly an active vasodilatation of the vessels of the nasal mucous membrane. Martin and Mendenhall (188), have confirmed the result of Tschalussow and demonstrated again the occurrence of an active vasodilatation in the nasal mucous membrane. They also showed that weak stimuli applied to somatic afferent nerves cause vasodilatation and strong stimuli vasoconstriction in the vessels of the nose. This makes it clear that these vessels share actively in the reflex changes in blood pressure. While admitting that strong stimulation of the vago-depressor nerve acts in an inhibitory man-

ner on the vasoconstrictor center, Martin and Stiles (189) and Martin and Mendenhall (128) do not agree with Bayliss' (129) theory that an inhibition of the vasodilator center occurs during pressor stimulation.

Martin and Stiles (130) have shown that when the vago-depressor nerve is stimulated it is possible to secure by the use of carefully graded stimuli two types of reflex fall of blood pressure. They found that the vago-depressor nerve in the cat has two thresholds. One of these is low like that for depressor reflexes from somatic nerves; and stimuli of this grade yield a moderate but transient fall in blood pressure which shows a tendency to recover within a period of thirty seconds. The other threshold is very high like that for pressor responses from the somatic nerves. Stimuli above this threshold yield a much greater drop which persists for a longer period. They attribute the first response to stimulation of the vasodilator mechanism and the second to an inhibition of the vasoconstrictor center. It would appear from the work of Martin and his associates that the threshold of the vasoconstrictor center is high both for excitatory and inhibitory afferent impulses.

Since it has been demonstrated that the depressor reflex involves an active vasodilatation as well as the inhibition of vasoconstrictor tone, there has been a tendency on the part of some authors to postulate the existence of afferent vasodilator fibers in addition to pressor and depressor fibers. Martin and Stiles (130) state that a given sensory nerve may contain both depressor and excito-dilator fibers or the same fibers may make central connections such as to mediate both reactions. The latter assumption seems the more reasonable.

Since the vasomotor mechanism is obviously intended to regulate the flow of blood through the several organs according to their varying needs at different times, one might assume that the various afferent nerves would possess special relations with the vasomotor centers whereby each could give its own particular type of vasomotor response which would differ in the localities affected from that caused by any other nerve. It is surprising that very little if any clear evidence of such a specific action has been obtained. Porter and Beyer (176) seem to be the only investigators who have attacked this interesting problem directly. They could however obtain no evidence that the depressor nerve forms special connections with the cells which control the vaso-motor fibers of the splanchnic nerves. In this their results agree with those of Bayliss (129), (175), Sollman and Pilcher (177), and Fofanow and Tschalussow (127). Porter and Beyer conclude that the fibers of the depressor nerve probably connect in the same way with all the cells in the bulbar vaso-

motor center and that there is no reason to suppose that other afferent vasomotor nerves differ in this respect from the depressor nerve. Afferent vasomotor fibers would thus influence all the bulbar vasomotor cells alike and the bulbar center would have no part in the distribution of the blood to the several organs or regions of the body. This question is so fundamental that it deserves further study.

A question allied to that just discussed concerns vasomotor summations. This has been considered by Martin and Stiles (189), (190) who worked with cats anesthetized with urethane. The fatigue which quickly cuts short the pressor response is on the afferent side. By successive stimulation of widely separated afferent nerves they could maintain the blood pressure at an increased height for many minutes. The superior reinforcing power of a distant nerve may be accounted for on the theory that its afferent connections with the center are unimpaired by previous use; or it might be supposed that it has access to a fraction of the central mechanism not previously stimulated and through this to a fresh set of vessels. Depressor summation is more pronounced when one of the afferent nerves excited is the vago-depressor trunk than when the summation is secured by stimulation of two afferent nerves other than the vagus. The antagonism between pressor and depressor influences is shown to have the character of algebraic summation. The after effect of pressor-depressor summations is typically a transient fall in blood pressure, suggesting that the depressor influence in masked but not destroyed by concurrent pressor excitation. In the opinion of Martin and Stiles the nature of this after-effect indicates that depressor and pressor influences act upon different parts of the central mechanism in such a manner that each exerts its normal effect in the presence of, but masked by, the other.

Vasodilator axon reflexes. An entirely new aspect has been given to the question of vasodilator phenomena by the researches of Bayliss (191), (192). His investigations show that the dorsal roots contain vasodilator fibers, which do not pass into the sympathetic chain nor degenerate when cut between the spinal cord and the ganglion. Since these fibers do degenerate when the spinal ganglia are excised, he regards them as being identical with the ordinary sensory fibers whose peripheral terminals must therefore serve both as sensory and as efferent vasodilator endings. He believes that in some, if not in all cases of reflex vascular dilatation of the limbs there is a production of antidromic nerve impulses in the posterior root fibers, that is to say, these fibers serve as the efferent limb of the vasodilator reflex arc. In their efferent capacity these fibers

do not concern us in this paper but a knowledge of their double peripheral connection is essential for an understanding of the axon reflexes that lead to local vasodilatation. This phenomenon was first carefully studied by Bruce (122). He found that the inflammatory dilatation of the conjunctival blood vessels, produced by a drop of mustard oil in the eye, is not affected by total section of the spinal cord nor of the dorsal roots proximal to the ganglion nor of the same distal to the ganglion unless time is allowed for degeneration. But if the sensory fibers are degenerated or if the part is under the influence of an anesthetic the vasodilatation does not occur. The peripheral sensory fiber must be blocked; the mere exclusion of painful sensation is not sufficient to eliminate the reflex. Bruce believes that the sensory nerve fibers divide peripherally into two branches one with a sensory ending the other with a terminal in the wall of a blood vessel. Local vasodilatation is an axon reflex through the two branches of the same fiber. These results have been confirmed by Januschka (193) and Bardy (194). The latter author found that the reaction was eliminated by suitable doses of nicotine and argues that the branch of the sensory fibers going to the blood vessel does not end directly in the musculature of the vessel wall but acts through the intermediation of a neighboring sympathetic ganglion cell. Richardson and Wyatt (195) extended the observations to the cutaneous nerves of the limbs. An increase in volume of the limb was obtained by stimulating the cut cutaneous nerves outside the plethysmograph or by stimulation of the skin inside the plethysmograph. Cocain applied to the skin eliminated the reflex from cutaneous stimulation. A clear statement of the known facts in regard to vasomotor axon reflexes has been given by Whelan (196).

Although the work of Bayliss and Bruce seems to have been amply comfirmed there are those who do not believe in the existence of a vasodilator axon reflex. Ebbecke (197) thinks that the centers for the local vasodilator reflexes are located within the corresponding segments of the spinal cord. Fofanow and Tschalussow (127) are of the opinion that the vasodilator fibers of the dorsal roots are of intraspinal origin. Stevenson and Reid (198) could find only minor differences between the reactions to mustard oil in the normal and anesthetic eye and say that their experiments give little support for the theory of an axon vasodilator reflex.

Pulmonary and portal vasomotor reflexes. Not much is known concerning the efferent side of the vasomotor control of the pulmonary and portal circulation and even less concerning the reflex control of blood

vessels in these teritorites. Henderson (199) and Hooker (200) have found evidences of vasomotor reflexes in the portal system; and Schafer (201) and Luckhardt and Carlson (202) have demonstrated that the pulmonary circulation may be influenced reflexly through the nervous system.

REFLEXES OF THE ALIMENTARY TRACT. The central nervous system has relatively little to do with the control of the movments of the stomach and intestines, which are regulated for the most part by the plexuses of Auerbach and Meissner. Since next to nothing is known about the structure of these plexuses and of the interrelations of the nervous elements which compose them the problems relating to the control of the movements of the alimentary tract are very baffling.

Gastric reflexes. As has been said, the movements of the stomach are primarily under the control of its intrinsic plexuses. When isolated from all extrinsic nervous connections and removed from the body the stomach adapts itself to the volume of its contents (203). Gastric peristalsis continues after large doses of nicotine have blocked the path from the central nervous system (204). According to Carlson (205) all the essential features of the hunger contractions are determined by the local neuromuscular mechanism; but these contractions may be modified and regulated through the gastric nerves. While the vagus exerts relatively little effect on the hunger mechanism, Rogers (206), working on decerebrated dogs with divided splanchnics, obtained spasmodic contractions of the entire stomach by the central stimulation of one vagus, the other vagus being intact. On the other hand, the splanchnics exert an inhibitory effect on gastric contractions and this inhibition is readily reinforced reflexly by afferent impulses from many sources. Carlson (207) found that stimulation of the gastric mucosa caused an inhibition of the tonus of the stomach and of the hunger contractions and demonstrated that this inhibition was in part dependent on the central nervous system. In this case the afferent impulses probably travel up the vagus. The contractions of the empty stomach may also be inhibited by stimulation of the taste buds and by the mechanical stimulation of the afferent nerve endings in the mouth caused by chewing indifferent substances (208). As shown by Cannon and Lieb (209) swallowing causes a receptive relaxation of the stomach which is dependent upon the integrity of the vagi. Reflex inhibition of the hunger contractions may be obtained from the intestinal mucosa. Brunemeier and Carlson (210) have shown that when the vagi and splanchnics are intact all mechanical and chemical stimulation of the upper part of the intestinal mucosa inhibits gastric

tonus and hunger contractions. But when these nerves are cut inhibition from the intestinal mucosa is less marked, has a greater latent period, and is of shorter duration. Hence cerebrospinal as well as local reflex paths are involved in this as in the similar response from the gastric mucosa.

Reflex gastric hypermotility may result from irritation of the gall bladder, duodenum or appendix and these organs may be assumed to be three of the possible foci of reflex gastric stimulation (211).

By means of the local reflex mechanism acid gastric contents causes an increased tone of the cardiac sphincter which prevents regurgitation into the esophagus (212). But the tone of this sphincter is also influenced by nervous impulses reaching it over long reflex arcs. Each act of swallowing is accompanied by a relaxation followed by an increased contraction of the cardia. In both cases the efferent path is in the vagus (203), (209). That this is a true reflex by way of the vagus is shown by the fact that Meltzer and Auer (213), secured the same relaxation followed by contraction of the cardia by central stimulation of one vagus while the other was intact. Clinical and experimental observations indicate that mechanical and chemical irritation of the region of the cardia, such as is produced by cold or carbonated drinks, produces an increased tone in this spincter (214). This is a vagal reflex and cannot be obtained after vagotomy.

The control of the intermittent discharge of food from the pylorus rests with the intrinsic plexuses (203), (215). When acid is allowed to stimulate the mucosa of the pyloric end of the excised stomach it causes the pyloric sphincter to relax. Acid in the duodenum causes increased tone of the sphincter but this does not occur if the serous and muscular coats have been divided between the pylorus and duodenum. Best and Cohnheim (216) found that introduction of acid into any part of the small intestine caused delay in emptying the stomach. High intestinal section and suture cause the pylorus to remain closed for several hours; and intense irritation of the colon caused by injecting croton oil into the cecum may cause delay in emptying the stomach; but Cannon (203), to whom we are indebted for these observations, does not state what nervous mechanism is involved. According to White (217), who studied by the roentgen-ray method the effect of stimuli from the lower bowel, delay in emptying the stomach is the exception and not the rule in lesions of the lower part of the intestine. Delay occurs only when the stimulation is very strong. White's results do not support Barclay's (218) theory of an ileopyloric reflex which prevents an overfilling of the small intestine.

Intestinal reflexes. All of the movements of the intestine persist after every extrinsic nerve has been divided. Excised portions of the small intestine or colon exhibit contraction above and relaxation below a stimulated point. Bayliss and Starling (220) first formulated this law of the intestine and showed that a local reflex was responsible for intestinal peristalsis. Magnus, (221) obtained the same coördinated response in a piece of excised gut from which the mucous and submucous layers had been removed along with the submucous plexus and thus demonstrated that the neural mechanism responsible for this reaction is located in the myenteric plexus. This justifies the name myenteric reflex given to this coördinated response by Cannon (222).

According to the last mentioned author, the myenteric reflex is responsible for the downward peristalisis that moves the food along the small intestine but not for gastric peristalsis nor for antiperistalsis and segmentation in the intestine. Intestinal segmentation like gastric peristalsis persists after the myenteric plexus has been interrupted by numerous circular incisions through the muscular coats (223), (224), and therefore represent a more strictly localized response than the myenteric reflex, which involves the transmission of excitatory impulses for some distance upward in the gut and of inhibitory impulses for even longer distances downward.

The capacity of the gut to exhibit rhythmic contractions disappears when the myenteric plexus is removed (221). This indicates that these rhythmic contractions are of nervous origin; but this conception of their genesis has been called in question by Gunn and Underhill (225). These investigators have obtained rhythmic contractions from isolated rings of the circular musculature of the cat's intestine which, according to their belief, were free from nerve cells. Their conclusion rests on the generally accepted notion that the nerve cells of the myenteric plexus do not penetrate deeply into the circular muscle. It should however be noted in this connection that Müller (226) has demonstrated the presence of many large ganglion cells in the outer third of the circular musculature of the frog's gut. Alvarez and Starkweather (227) think that the preponderance of evidence now points toward the myogenic origin of the rhythmic movements of the intestine and say that the law of the intestine as formulated by Bayliss and Starling is so often in abeyance that it cannot be the chief factor in controlling the onward movement of the intestinal contents. As a rule in their experiments they could not obtain the myenteric reflex. The typical response was an increase of tone and amplitude in both directions from the stimulus; but conduction of the

impulse was somewhat better in the aboral direction (228). Since they obtained the myenteric reflex most often as a response to distention of a balloon in the gut it is possible that the reflex may be a reaction to distention and not to other forms of stimuli. They claim to have demonstrated a metabolic gradient in the intestines, as a result of which the irritability and rhythmicity of the gut decreases from the duodenum to the colon and believe that this rather than the myenteric reflex is responsible for the direction of peristalsis.

It thus appears that several factors enter into the control of the movements of the gastro-intestinal tract even after all extrinsic nervous control has been eliminated.

1. An arrangement of the elements in Auerbach's plexus in such a manner as to permit of a coördinate reflex response to a local stimulus involving contraction above and relaxation below the stimulated point. Illustrations of the action of this mechanism are found in peristaltic contraction waves which are preceded by relaxation and in the acid control of the cardia and pylorus.

2. There is probably a mechanism for more strictly local responses which according to Cannon is responsible for rhythmic contractions, segmentation, gastric and colic peristalsis and antiperistalsis of the colon.

3. It now appears possible that many or all of the strictly local responses may be explained on the basis of myogenic contraction.

The little which we know at present concerning the structure of the submucous and myenteric plexuses does not aid us in interpreting these physiological problems. The histology of these plexuses has been investigated particularly by Dogiel (229), L. R. Müller (230) and R. Müller (226). The last mentioned author describes the plexuses as consisting of a true nerve net. Assuming that Müller is correct such a simple nerve net could be invoked to explain any neurogenic response of the isolated intestine except the myenteric reflex, for which specialized conduction paths are required.

The occurrence of even a local reflex requires the presence of receptive or sensory nerve elements. There is no evidence for the hypothesis that the nerve cells of the gut receive afferent impulses through some of their processes and send out motor impulses by others. We do not know to what extent the individual nerve cells of the gut serve sensory or motor functions. In the myenteric, but not in the submucous plexus, Müller (230) could differentiate two types of cells. Those ganglion cells which lie free in small lacuna and which give off numerous processes from all sides are to be distinguished from those which lie close to the musculature

and give off small dendrites to it. He suggests that the latter may be motor cells and the former sensory. In order to prove the sensory character of any of these cells it would be necessary to demonstrate the connection of their processes with the epithelium of the gut or with definite sensory endings in the gut wall. This he could not do. Dogiel (30) was able to trace dendrites from cells in the myenteric plexus which he regarded as sensory to the mucosa and his pupil Sakusseff (231) claimed to have traced fine twigs from the intestinal plexuses to the mucosa of the gut of fishes. These ramified beneath the epithelium and sent fine varicose threads into the columnar epithelium where they ran between the epithelial cells and formed a network about individual cells. If these observations could be confirmed—and more than 25 years have passed without their confirmation—the sensory limb of the intestinal reflex arc would be demonstrated.

Our information regarding the innervation of the gastric mucosa is not much greater. Müller (226) was able to trace nerve fibers to the epithelium of the frog's stomach and saw them divide repeatedly, some of the branches entering between the basal tapered ends of the epithelial cells. This is largely confirmatory of the observations of Smirnow (232) who was able to trace similar fibers into the epithelium. None of these observations are such as to excite great confidence and at present one is justified in taking a skeptical attitude toward all of them. There are no observations which would indicate the presence of sensory cells in the epithelium, sending fibers into the enteric plexuses, such as those which form a characteristic feature of the cœlenterate nervous system. It is obvious therefore that at the present we are not justified in thinking of the enteric plexuses in terms of the nerve net of cœlenterates because it has not been demonstrated that these plexuses are truly composed of a nerve net and because sensory elements like those of the cœlenterate apparently do not exist in the gut.

In spite of the negative character of the histological evidence the existence of sensory fibers in the gastro-intestinal mucosa has been assumed by most physiologists. And indeed receptive endings in the epithelium seem to be required by the fact that responses may be obtained from both chemical and mechanical stimulation of the mucosa. The acid control of the cardia and pylorus (203), the inhibition of hunger contractions by introduction of various fluids into the stomach (205) variations in the rate of passage of different kinds of food along the intestinal tract (203) and other phenomena indicate the presence of chemical sensibility in the gastrointestinal mucosa. The experiments of Babkin (234) em-

phasize the importance of chemical as opposed to mechanical stimuli. But the mucosa is also sensitive to mechanical stimuli as is shown by the inhibition of hunger contractions in the stomach by gently rubbing the mucosa of the intestine with a glass rod (205) and by the increased intestinal peristalsis caused by branny foods (203). But mechanical stimulation of the gastric mucosa is not sufficient to produce a reflex secretion of gastric juice (235). Exner (236) claims that pressing a pointed object against the mucosa causes a contraction of the musclaris mucosae resulting in a slight indentation of the surface at the stimulated point.

Observations made by Short (237) on a case where the ileocecal valve was exposed to view as a result of cecostomy indicate that the valve acts like a sphincter and is subject to reflex control from the stomach. Short says that it relaxes in from two to four minutes after food is taken into the stomach and continues to discharge fecal matter in gushes for about one hour. Local stimulation of the mucosa of the cecum in the region of the valve when the orifice was in full activity served to delay but not to stop the passage.

Reflexes through the cerebrospinal axis play but a minor rôle in the regulation of intestinal movements. Reflex inhibitions are however not difficult to obtain. By graphic records Hotz (238) was able to show that stimulation of any peripheral sensory nerve leads to inhibition of intestinal movements through the spinal cord and splanchnic nerves. For example, dissecting away the skin from the abdomen or leg or immersion of the lower half of the body in warm salt solution inhibits peristalsis (239); and according to Cannon and Murphy (240) crushing of the testicle also causes a reflex dynamic ileus. The last mentioned observers found that the stasis resulting from handling of the stomach and intestines was a purely local reaction not affected by section of the splanchnics.

By far the best account of the cerebrospinal reflexes affecting the intestines has been given by Lehmann (241), who also gives a good review of the previous work on this subject. The only response of this kind which it has been possible to demonstrate in the small intestine is one of inhibition. Intestinal movements may be stopped by stimulation of the central ends of the hypogastric, splanchnic and vagus nerves. Sciatic stimulation causes arrest of the pendulum and later of the peristaltic movements of the gut and usually a decrease of tonus. Since this sciatic reflex does not occur if the splanchnics are divided nor if the spinal cord is transected in the upper thoracic region, the center must be in the medulla oblongata and the efferent path in the splanchnic nerve.

Stimulation of the central end of the hypogastric nerve causes a similar inhibition; but in this case the center is in the thoracic portion of the spinal cord since section of the cord at the height of the first thoracic vertebra does not obliterate the reflex, and section at the level of the first lumbar vertebra does.

Stimulation of the central end of one splanchnic inhibits peristalsis and sometimes causes a dilatation of the gut; but this effect disappears when the remaining splanchnic is cut. Since high thoracic section of the cord does not eliminate this response the reflex arc is complete in the cord.

The vagus yields through the cerebrospinal axis and splanchnic nerves an inhibition of peristalsis with or without decrease in tone of the intestinal musculature.

Defecation. From the large intestines more complicated reactions can be obtained (241). Stimulation of the sciatic nerve causes contraction of the colon and rectum and relaxation of the internal sphincter, a complex which will be referred to below as the defecation reflex. The efferent path for this reflex is in the visceral branches of the sacral nerves, and the center is in the medulla oblongata since the effect is obliterated by section of the spinal cord at any level.

Central stimulation of the visceral branches of the sacral nerves or of the hypogastric nerve usually causes reflex dilatation of the colon and rectum and contraction of the internal sphincter, and this reaction can be obtained after transection of the cord at the level of the first lumbar vertebra. Central stimulation of the splanchnics produces inhibition of the rectum and contraction of the internal sphincter and this effect can be obtained after transection of the cord at the level of the first thoracic segment.

Central vagus stimulation produces the defecation reflex. From these observations of Lehmann it is obvious that central stimulation of the vagus and somatic sensory nerves produces movements of defecation, while central stimulation of the splanchnic, hypogastric and sacral visceral nerves exerts predominately an inhibitory influence. It is also evident that there are spinal as well as bulbar centers for intestinal reflexes, and that the spinal centers are concerned with inhibitory reflexes.

It should be added that Lehmann found that strong stimulation of the abdominal splanchnic nerves occasionally called forth the defecation reflex. It is surprising that it is not easier to obtain this response from the nerves to the large intestine, since according to Cannon (203) and Müller (230) the reflex is normally excited by the entrance of feces into the

rectum and since Merzbacher (242) has shown that after section of the lower lumbar and sacral dorsal roots normal defecation does not occur.

Although under normal conditions a voluntary factor, contraction of the abdominal muscles, enters into defecation the results of Goltz (243) cited in *Der Hund ohne Grosshirn* shows that it can be carried on as a pure reflex. It should also be noted that while defecation usually involves a reflex through the spinal cord, destruction of the lumbar and sacral cord results in a temporary diarrhea lasting several days and followed by normal evacuation of the large intestine at the customary intervals (244). Although the results of destruction of the spinal cord may vary in different animals (245), it would seem that when the gut is freed from all spinal control, inhibitory as well as motor, the local nervous system of the gut is able of itself to control defecation (260).

According to Müller (230) voluntary inhibition of defecation is brought about by the contraction of the muscles of the pelvic floor; and sensory impulses arising in these contracted muscles reflexly inhibits the activity of the colon and rectum.

Swallowing. Deglutition involves a series of consecutive movements of the floor of the mouth, pharynx, esophagus and cardia and is under the control of a complicated reflex mechanism, which has been carefully studied by Meltzer (248). This progressive series of movements may be initiated by stimulation of the pharyngeal mucous membrane. Certain spots lying in the direct path of the food are more sensitive than others and have been called "chief spots" by Kahn (249). These areas vary in different animals—the back of the pharynx in dogs and cats and the tonsilar region in monkeys—but they all appear to be in the territory of the glossopharyngeal nerve. Kahn also identified secondary spots on the upper surface of the soft palate, supplied by the glossopharyngeal and trigeminal nerves, and on the dorsal surface and base of the epiglottis, supplied by the vagus nerve. These observations have been confirmed by Miller and Sherrington (250). It is usual therefore for the swallowing movements to be initiated by afferent impulses traveling along the glossopharyngeal nerve. After intracranial section of both trigemini swallowing could still be elicited from the posterior part of the tongue and from the pharynx and seemingly as readily as when these nerves were intact (250). Stimulation of the central stump of the glossopharyngeal and superior laryngeal nerves excites swallowing (249), (250). Weak stimulation of the glossopharyngeal nerve is said by Kitajew (251) to inhibit while strong stimulation excites swallowing movements. Stimulation of the central end of the lingualis-chorda tympani trunk also inhibits swallowing (250).

When once initiated the entire train of movements follows in correct sequence without the necessity for any intercurrent sensory impulses from the parts traversed by the bolus of food. This conclusion is based on the observations of Kronecker and Meltzer (252) and Meltzer (253) who showed that even after removal of a whole ring of esophagus the peristalsis once begun would appear again in the lower end of the esophagus.

Another and secondary reflex mechanism of deglutition can be demonstrated when food is introduced directly into the upper part of the esophagus without stimulating the mucosa of the pharynx. Food so introduced initiates a peristaltic wave running down the esophagus with relaxation followed by contraction of the cardia just as in normal deglutition. But in this case ligature of the esophagus interrupts the peristaltic wave. That the response to food introduced into the esophagus is a true reflex is shown by the fact that it disappears after section of the vagi. Meltzer (248), (254) to whom we owe these instructive experiments, concluded that this secondary mechanism depended on a succession of reflexes through the vagus, each initiated by the contact of the bolus with successive portions of the esophageal mucosa. In line with this idea is the observation that stimulation of the central end of one vagus produces reflexly through the other vagus a contraction of the entire esophagus (255).

The afferent limbs of the reflex arcs concerned with swallowing are therefore found in the glossopharyngeal and vagus nerves, the afferent fibers of which enter the tractus solitarius in the medulla. It would seem that these same fibers may be stimulated by unipolar faradization of the fovea inferior in the floor of the fourth ventricle and that typical swallowing movements may be produced in this way (250).

Unilateral stimulation of the superior laryngeal nerve or of the pharyngeal mucous membrane normally causes bilateral swallowing movements. But if the medulla oblongata is split in the median plane at the level of the nuclei of the glossopharyngeal and vagus nerves contraction of the suprahyoid muscles can be obtained only on the side of the stimulus (256). This is probably due to cutting of the crossed secondary afferent fibers from the nucleus of the tractus solitarius.

All of the swallowing movements so far described are reflexes mediated through the medulla oblongata; but Cannon (203) has shown that after the section of both vagi the lower end of the esophagus, which contains smooth muscle, regains in a few days the capacity to respond to the presence of a bolus of food by a downward peristalsis. This is a purely local reaction executed by the intrinsic nerve plexuses of the gullet.

Vomiting is a complex reflex in which the stomach plays a relatively passive rôle. There is relaxation of the cardia and of the cardiac portion of the stomach; and the gastric contents are expelled through the esophagus by the sudden and simultaneous contraction of the abdominal muscles and diaphragm (203). It commonly results from abnormal stimulation of the sensory endings of the vagus nerve in the stomach, and can be produced in cats by electric excitation of the gastric vagus (257). It can under certain conditions also be induced by stimulation of the pharynx and upper part of the esophagus.

Valenti (258) has demonstrated that stimulation of the mucosa of the pharynx and upper part of the esophagus leads reflexly to a dilatation of the cardia and that cocainization of this region causes the cardia to exhibit more than the usual degree of tonic contraction. When the area of mucosa in question is fully anesthetized the cardia is so tightly closed that none of the stomach contents is expelled into the esophagus by the vigorous contractions of the diaphragm and abdominal muscles induced by apomorphine. Thus there is brought into play in vomiting a reflex from the mucosa of the pharynx and esophagus which is necessary for the dilation of the cardia and the escape of stomach contents. This explains at least in part why stimulation of the pharynx will under certain conditions excite vomiting. The afferent path for this reflex is in the glossopharyngeal nerve; and sections of this nerve on both sides of the neck is sufficient to prevent the expulsion of the stomach contents although all the other elements of the vomiting reflex occur as in the normal animal. More recently Valenti (259) has shown that the vagus contains some of the afferent fibers and all of the efferent fibers of this reflex arc.

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THE PHYSIOLOGICAL EFFECT OF UNDERNUTRITION

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Diogenes Laertius states that the philosopher Heraclitus (born about B.C. 435), despairing of mankind, retired to the mountains where he lived entirely upon vegetables and herbs, became dropsical, and died. In the year A.D. 586, when famine desolated France, a similar diet produced edema and death. Gaspard (16), who records the above, also describes famine and death in Guadaloupe among 4000 negroes, who became completely hydropic upon a diet of plants and mallow herbs.

Gaspard also carefully describes the disastrous famine which overwhelmed west central France in 1817, and which he personally witnessed. During the first three months of the year the inhabitants lived on potatoes, oat bread, bran and other poor foods. When these resources were exhausted the unfortunate people were reduced to existing upon the pasture of animals. Materials such as the oyster plant, wild sorrel, nettles, the patience dock, chicory, thistles, the peelings of tender branches, etc., formed their dietary. This herbage was hashed, cooked and thereby reduced to a pulp, as is commonly done with spinach and sorrel. Such a diet, when constantly taken, always resulted in dropsy of the cellular tissues, without ascites, without icterus, without organic lesions of the liver or other abdominal viscera. Many women stated that their menses ceased. It was later found that the number of conceptions during this period was less than half the number which occurred during the corresponding months of the preceding and following years. The dropsical condition continued throughout the entire period of the use of this diet and did not disappear until the harvest season restored normal human food. For months or even years thereafter some of the individuals exhibited swollen abdomens, or edema of the face, of the legs or of the feet.

Those who were the least vigorous or who had subsisted longest on this diet of herbage died on account of it. Sometimes they perished of starvation at the roadside. Others died, not of famine, but from a kind of indigestion caused by a gluttonous indulgence in barley bread when this became available at the time of the new harvest.

The siege of Paris (54) from September 19, 1870, to January 28, 1871, imprisoned for over 4 months two million French people who endured extreme privation. Especially the old people and the children perished from want of suitable food, the lower classes undergoing untold miseries of hunger and cold. Two months before the end of the siege the supplies of milk and meat were practically exhausted. During the last 10 days bread was rationed at the rate of 300 grams per day per person, with half rations to children under five. The bread contained 30 per cent of flour. "The quality is horrible, black, heavy, miserable stuff, made of flour, oatmeal, peas, beans and rice." Cats, dogs and rats were eagerly devoured. The death rate reached 4465 weekly, or at the rate of 116 per 1000 per annum. Scurvy broke out on account of the dominant diet of bread and rice. Delpech (8) states that the presence of scurvy was directly traceable to the absence of fresh vegetables. In one prison, out of 250 prisoners, 65 had scurvy, of whom 11 died. On January 23, the 127th day of the siege, mobs of poor, starving people were in the streets crying "Donnez nous du pain." The capitulation of the city followed 5 days later upon the complete exhaustion of the food supply. During the 2 weeks following the armistice the death rate averaged 4561 per week in contrast with 1122 per week during the corresponding weeks of the year previous (41).

The following picture of the onset of undernutrition in Germany during the war of 1914–1918, is presented by Rubner (49). The blockade was at first inefficient and there was no change from the normal food supply until April, 1916. For the winter of 1916–1917 the department of food supplies planned to provide rationed foods in amounts which may be contrasted with the quantities actually furnished, as follows:

	AS PLANNED			AS ACTUALLY PROVIDED		
	Amount	Protein	Calories	Amount	Protein	Calories
		grams			*grams*	
Bread	271.0 gm.	17.2	688	271.0 gm.	17.2	688
Potatoes	710.0 gm.	14.9	710	357.0 gm.	7.5	341
Butter and margarine	18.0 gm.		140	11.4 gm.		89
Milk	200.0 cc.	6.8	111			
Meat	70.0 gm.	10.7	158	36.0 gm.	4.5	78
Eggs (per piece)	0.3	4.2	53	0.07	1.0	13
Sugar	32.0 gm.		125	26.0 gm.		104
Cereals				9.8 gm.	0.9	31
Totals		53.8	1985		31.1	1344

The reduced allowance was not everywhere obtainable. In the cities only a third of the quantity of meat allowed was distributed, and in mid-winter 2.5 kgm. of turnips weekly were substituted for a ration of 2 kgm. of potatoes. Additional unrationed foods could be purchased at high prices.

The exclusion of animal foods from the diet made it monotonous, and for the many it was no better than the fare of prisoners sixty or seventy years before. Garnishings, spices, in short all things which might have served to improve the flavor of the food, were lacking. Soups, vegetables, and above all, turnips were the dominant note. The chief characteristic of this diet was its high water content, due to the absence of fat, which was replaced by carbohydrate foods. Such foods, with the exception of bread, are largely diluted with water. Sugar, which usually serves to concentrate the food value of many dishes, was allowed in too small quantities to be of much service.

Rubner remarks that the first result of an insufficient diet is a decrease in the efficiency of laborers. This is evidenced by the fact that fatigue comes on more quickly than usual. Not only is there a decrease in the muscular efficiency of paid laborers, but also in people living sedentary lives; the muscular activities which are concerned with the normal preservation of health become restricted. The love of roaming and of sport is lost, children cease to play, and a person avoids as far as possible all bodily exertion. The mood of the individual affects the result. Thus one may, by special effort, overcome the sensation of fatigue for a certain number of days in order to accomplish a definite result, as does the soldier who advances by magnificent forced marches in anticipation of victory. But this is a very different matter in comparison with the accomplishment of work in the dull, monotonous daily grind of civilian life. During the war certain Italian farm laborers, receiving 450 grams of flour daily, accomplished their work. When this ration was cut to 250 grams they refused to work.

The same apathy is true as regards mental work. The love of accomplishment, the power of performance, the note of personal initiative are absent, which impulses under ordinary conditions increase the assimilation of food and favor muscular energy. As the mind becomes depressed, muscular movements become slow and listless. It is related that a distinguished mathematician of Leipzig, in order to conserve his food requirement, remained in bed most of the day, doing his intellectual work while in bed.

Rubner estimates that the amount of nourishment which should be taken daily by an average adult contains: Calories, 2569; Protein, 91 grams. The official ration offered, in contrast, only one-half the calories and one-third the protein required. Furthermore, bread made from wheat milled at 95 per cent extraction showed a loss of 40 per cent of its nitrogen in the stools, even in strong, healthy men accustomed to rough fare. A bread intended for the use of prisoners and made of rye, maize, and potato-flour showed a loss of 47.3 per cent of its nitrogen in the feces. The mixed diet of peace time showed a loss of 10 per cent of nitrogen, while the coarse, vegetarian war diet showed that 20 or even 50 per cent of the nitrogen of the diet could not be absorbed.

Life under these conditions, Rubner estimated, caused a reduction in body-weight among those of the urban population who were over 25 years of age from an average weight of 60 kgm. to one of 49, or a loss of very nearly 20 per cent.

The Prussian authorities estimated the increase in the civilian death rate as follows:

YEAR	NORMAL = 100	DEATHS ABOVE THE NORMAL RATE
1913	100	
1914	100	
1915	100	
1916	114	
1917	132	260,000
1918	137	294,000

On this basis 800,000 deaths were computed as ascribable to the blockade and its consequences. The validity of the interpretation requires assessment, but it is certain that under-nutrition diminished physical and mental power, reduced resistance to disease, and also that the evils of the time were furthered by lack of warm clothing, lack of coal for heating purposes, and to extreme mental excitement.

It will be recognized from the above general descriptions of partial famine that it is akin to the undernutrition among the poor of large cities prior to the war.

Protein metabolism. The functional activity of living matter is primarily due to the arrangement of protein in protoplasm. A wasted organism, with diminished muscle tissue, is a characteristic result of protein undernutrition. The minimum quantity of protein destruc-

tion in the human being is to be found after giving, during a long period of time, a diet containing sufficient calories, at least one-third of which must be in carbohydrate, preferably in sugar, but which contains no protein. The urinary nitrogen may thus be reduced to only 2.2 grams daily or even less. This level of protein metabolism has been termed by Rubner the "wear and tear" quota of protein metabolism. More recently he (50) has defined it as being the zero point of protein metabolism.

The "wear and tear" quota includes the protein required for the growth of the hair, nails, epidermis and epithelia; it includes the losses through the digestive juices and through the wear and tear on all the organs of the body, especially the daily destruction of protein involved in the demolition of the cellular elements of the blood. It is increased in menstruation, pregnancy and lactation, but is unchanged in old age.

Muscular work is without influence upon this factor.

Rubner calculates that the "wear and tear" quota of protein metabolism corresponds to 0.044 gram of nitrogen per kilogram of body weight daily, or 0.0303 mgm. per minute, an infinitesimal quantity. Since a well-nourished man of 70 kgm. contains approximately 2100 grams of nitrogen, and the wear and tear quota corresponds to about 3 grams of nitrogen daily, one may estimate an inevitable daily loss of 0.14 per cent of the total body protein, unless food protein is furnished with which to repair the machine, to replace the worn-out parts.

Rubner states that under certain conditions a diet containing only 4 grams of protein nitrogen will protect the body from losing protein nitrogen, consequently 1 gram protein may protect 525 grams of body protein from loss of substance. However, should the protein in the diet contain only 3 grams of nitrogen, then on the first day of the diet 1 gram of body protein N would be lost; thereafter the nitrogen loss would be constantly less until finally equilibrium would be reached with 3 grams. Assuming the mean loss during this period to have been 0.5 gram of nitrogen daily and the total loss 525 grams, it is obvious that it would require 1050 days or nearly 3 years to deplete the body of a quarter of its protein store. Biologically the nitrogen minimum is a protective mechanism of the cells against their destruction. This is an important theoretical conception of Rubner's clear-visioned, scientific mind.

To accomplish nitrogen equilibrium at a low level of nitrogen intake it is necessary to provide protein of a chemical composition similar to that of the protoplasm which is being disintegrated. It is in this

particular that a dietary may lamentably fail. For this reason meat and more especially milk are sought. Rubner, in a personal letter to me, states that the decline in the health of the German people was coincident with the falling off of the milk supply (see p. 547). During (11) has written of the importance of the milk question in Austria. He makes the striking statement that the milk supply of Germany in normal times had nearly twice the monetary value of the output of all the German mines, inclusive of coal.

The loss of body protein. A characteristic of undernutrition is a prolonged loss of body nitrogen when the caloric content of the food is insufficient to cover the needs of the individual. This was first indicated by the work of Landergren (35).

Of striking interest and importance in this connection is the work of Jansen (27) upon normal and healthy medical students occupied in the Munich medical clinic of Friedrich Müller. Fifteen such individuals were given the official food ration containing 1600 calories and 60.6 grams of protein (9.7 grams of N). Nitrogen balance experiments were carried out upon them for between 6 and 31 days during March, 1917. Prior to the experiments the men had been for some time on short rations, especially as regards the protein element. The average loss in weight since the beginning of the war had been about 5 kgm. The average weight of the subjects was 62 kgm. While partaking of the above dietary the men lost weight daily and also about 2 grams of body nitrogen. This loss could be attributed to a deficiency of calories in the diet, for the addition to the diet of 500 calories in the form of milk-sugar resulted in the maintenance of body weight as well as of nitrogen equilibrium. Also, withdrawal of 900 calories in the form of carbohydrate from the official ration produced an even greater loss of body protein than when 1600 calories were given. These relations are shown on the following page.

Benedict (4) and his co-workers independently made the same discovery. Benedict selected a number of healthy young men inclined to athletic prowess, some of them over-weight for their height, and set about to reduce their weights about 10 per cent. The kind of food taken was an average mixed diet but in lesser quantity than was taken by other men not on the "diet squads." A typical diet sufficient for the maintenance of body weight contained 2559 gross calories and 12.85 grams of nitrogen. A typical day's ration on the reduced diet contained 1555 gross calories and 8.78 grams of nitrogen, of which 3.27 grams were of animal origin.

Influence of the official ration of Munich, March, 1917, upon the protein metabolism of medical students

	AGE	SEX	WEIGHT	DAILY CHANGE IN WEIGHT	FOOD		N IN URINE AND FECES	N BALANCE
					Calories	N		
			kgm.	*grams*		*grams*	*grams*	
1	32	M	57.6	−250	1632	9.72	11.97	−2.25
				+ 0	2105*	9.74	10.29	−0.56
4	23	M	67.0	−250	1630	9.61	11.74	−2.13
				+200	2027*	9.54	9.75	−0.21
12	21	M	63.5	−350	1616	9.89	12.63	−2.74
				+280	2107*	9.65	9.79	−0.14
5	22	M	64.6	−400	1624	9.72	11.29	−1.58
				−200	730†	10.59	14.74	−4.15
9	22	F	61.3	−500	1630	9.61	11.81	−2.20
				−350	736†	10.59	13.77	−3.19
10	25	F	60.4	−380	1630	9.61	9.93	−0.33
				−420	735†	10.59	13.41	−2.81

* Plus 500 calories in milk-sugar.
† Minus 900 carbohydrate calories.

Twelve men (squad B) partook during one week of a diet containing 1534 gross calories, daily eliminated 115 in the feces, 84 in the urine, and therefore utilized 1336 calories, or 87 per cent of the gross energy ingested. They took 8.21 grams of nitrogen, of which 0.89 gram appeared in the feces, leaving 7.32 grams or 89 per cent for other distribution. The protein of the diet was therefore normally digested.

During a period of 3 weeks the twelve men (squad B) partook of food which yielded 1375 utilizable calories and contained 8.19 grams of nitrogen daily. The nitrogen of the urine and feces averaged 11.29 grams per person. Hence, protein containing 3.10 grams of nitrogen, or approximately that present in 100 grams of lean meat, was lost daily from the bodies of these persons during the period of this low caloric intake. This would amount to a loss of about 2.1 kgm. of such protein-containing tissue in 3 weeks. The average loss in weight, however, was 4.4 kgm. or 6.5 per cent of the original body weights. If one calculates that a kilogram of body weight contains 30 grams of nitrogen, then 67.9 kgm., the average original weight, contained 2037

grams. If of this 65 grams were lost from the body, the loss of body nitrogen would have been only 3.2 per cent of the total original quantity present. The body weight had fallen much more rapidly, indicating a removal of fat and water content from these heretofore well-nourished individuals.

Another group of individuals (squad A) underwent a more prolonged and a greater reduction. During 4 months the greatest average loss of body weight in five individuals amounted to 11.2 per cent and, according to the principle enunciated above, it may be calculated that these five individuals, whose loss of body nitrogen was determined during 86 days, averaged 166 grams each or 8.1 per cent of their original nitrogen content. This calculation is imperfect on account of lack of dietary control on Sundays and during the Thanksgiving and Christmas holidays when protein could have been added to the body.

It has long been known that in the last stages of fasting an animal, having exhausted its stores of fat, may subsist upon its previously well-protected protein supply. Conditions analogous to these are reported by Loewy (58) in experiments upon himself. Weighing 64 kgm. in 1914, he lost 12.75 kgm. during 3 years of war or 20 per cent. When taking a diet of 1500 to 1800 calories, containing 7 to 8 grams of absorbable nitrogen, his urine contained on successive days 12.6, 15.6, 12.5, 15.1, 17.0, 16.5 grams. The great waste of body protein of which this was the proof and the physical and mental depression the portent, was entirely stopped by the addition of 200 grams of butter fat to the daily ration. Body protein had been attacked in the absence of any other available source of energy.

Retention of protein. An organism which has been depleted of its protein shows a great avidity for protein deposition when occasion offers. This was long ago shown by Rubner for the dog. Kestner (29) reports results obtained by adding 100 to 120 grams of meat to a hospital diet administered to patients who had suffered from extreme protein hunger. The following example may be cited: Patient J; weight 51 kgm.; slightly nervous female; of ruddy appearance.

	N IN DIET	URINE N	FECES N	± BODY N
Hospital diet (average of 4 days).. ...	8.0	4.5	2.2	+1.3
Hospital diet + 100 to 120 grams meat (average of 3 days).....	13.2	4.25	2.2	+5.75

In this case the whole of the protein of the meat was deposited in the depleted cells of the body.

Kohn (32) reports that a woman laboratory helper weighing 47 kgm., who suffered from chronic undernutrition in its most severe form, partook on one day of a diet containing 826 calories and 1.04 grams of nitrogen, and the *loss* of body nitrogen amounted to 2.57 grams. The addition of a bit of cheese, which raised the nitrogen of the diet to 5.23 grams, caused a *gain* to the body of nitrogen amounting to 1.97 grams on the day following. The animal protein of the cheese not only prevented a loss of 2.57 grams of body nitrogen, but was also sufficient to be seized upon for constructive purposes by the famished cells of the organism.

The urine of the undernourished patient of Kohn showed no abnormalities in the relative distribution of nitrogenous constituents (33).

Fürth (15) finds, however, that the presence of a gram of nitrogen in the urine of people suffering from chronic undernutrition is accompanied by a relatively high caloric value of the dried solids of such urine. The caloric quotient $\frac{\text{Calories}}{\text{N}}$ was between 9 to 13.3. Since this quotient for urea is 5.42, for uric acid 8.22, for creatinin 11.40, Fürth infers the increased presence in the urine of oxyproteic acids (quotient 38.0) and hippuric acid (quotient 72.4).

Oxyproteic acid is a characteristic urinary constituent when body tissue is being destroyed, and hippuric acid occurs when benzoic acid compounds are present, as in a predominantly vegetarian diet.

Von Hoesslin (22) shows the very great and continued capacity of an extremely undernourished person to appropriate food protein for the development of body tissue. An adequate quantity of food protein is desirable for this purpose, as well as an adequate intake of calories. The following table represents the results obtained upon a person during a period of four weeks. Values are given for 24-hour periods:

	FOOD INTAKE PER DAY			EXCRETA N PER DAY	N TO BODY PER DAY
	Protein	Calories	N		
	grams		*grams*	*grams*	*grams*
First week	62	1744	10.1	7.8	+2.3
Second week	57	2529	9.1	6.6	+2.5
Third week	92	1928	14.8	8.3	+6.5
Fourth week	98	2161	15.6	8.9	+6.7

This represents an addition of 124 grams of nitrogen to the body in 4 weeks.

The avidity with which tissues depleted of protein appropiate new protein for constructive purposes has been frequently observed after wasting disease, and a kindred property is also possessed by the tissues of growing infants.

The energy metabolism. The dietary prescribed by Carl Voit for an average laboring man contained about 3000 available calories. During the war the English came to the conclusion that the requirement of the average adult man was 3000 utilizable calories. Allowing for loss through transportation, marketing and spoilage, 3300 calories were estimated as the basis for the calculation of necessary national supplies. These figures were adopted as standard by the Interallied Scientific Food Commission, which also fixed the following relative food values when estimating the needs of a family:

Man	1.00	Child 10-13 years	0.83
Woman	0.83	Child 6-10 years	0.60
Boys over 13 years	1.00	Child under 6 years	0.50
Girls over 13 years	0.83		

A recent (1921) study of the diets of the working classes of Vienna by Gibbon and Ferguson (17) shows that the average dietary contains only 2064 calories "per man" per day instead of the necessary 3000.

Forty-nine families were investigated. The lowest energy value was 1269 calories. The fat was taken mostly in the form of margarine. Relief agencies contributed about 500 calories, or about one-fourth of the daily intake. Children between 2 and 3 years of age were 26.5 per cent under normal average weight and 13.6 per cent under the average normal height. Rickets was found in 29 families the caloric intake of which averaged 1885 calories "per man" per day, but was absent in 20 families which partook on the average of 2325 calories "per man." The writers observe, "It is hopeless to expect from a population on such diets the initiative and vigor by which alone the country can be saved from ruin."

Among German farmers O. Blum (7) found no reduction in body weight during the first 3 years of the war, for they received 3200 calories and 101 grams of protein. The men workers in a small town, on the contrary, lost 12 per cent in weight and the women workers 7 per cent, their dietaries having fallen to 2200 calories with a protein content of 54 to 75 grams. This work is confirmed by Loewy and Brahm (36) who showed that at a time when the poor in the cities were receiving 25 to 50 grams of protein and 1400 to 1800 calories and

were losing weight and body protein, country people were doing well upon a diet of bread and potatoes with small amounts of meat, milk and cheese, containing in all 3500 calories and 100 grams of protein. They state that their findings prove that their peace-time conclusions regarding the quantities of food required for human nutrition were correct.

Friedrich Müller, commenting upon this situation writes:

> Naïvely thinking man eats food without mental consideration, still less without giving ear to the current nutrition doctrines of Liebig, or Hindhede, or Ragnar Berg, but rather like a wild animal he follows his instinct until he is fully satisfied. He considers himself wrongly dealt with when he is prevented from doing this. It is therefore natural that the self-provider should take care of himself first, of his children, his relatives, his servants, and his cattle, and that he should anxiously hoard for the future.... In times of need the struggle for existence takes inconsiderate forms, the interest of individuals clash, and hand in hand with these conditions the moral sense and the sense of right and wrong are lowered.

Most of the food difficulties of Germany occurred in middle-class families, such as teachers, business people and pensioners who could not demand and receive the enormous pay of common laborers.

In German institutions such as prisons, prison camps and insane asylums, the conditions were worse than among those who were free to struggle to obtain foods in excess of the official rations. In such institutions reductions of 20, 30 and even 46 per cent of the original weight were observed as the result of continued restriction to the official ration, which was inadequate for the maintenance of body weight (42). One report ran "The inmates are all dead."

The effect of emaciation upon the energy metabolism. Magnus-Levy (39) first pointed out the great reduction in the heat production which takes place as the accompaniment of emaciation. The results may be briefly recorded in the following table:

	WEIGHT	METABOLISM 24 HOURS	CALORIES PER SQUARE METER PER HOUR (DU BOIS HEIGHT-WEIGHT FORMULA)	REMARKS
	kgm.	*calories*		
Extreme emaciation	36.2	835	26.6	Low diet
Emaciation	38.0	1077	33.0	Liberal diet
Rehabilitation	52.2	1486	40.5	Liberal diet

It is evident that the reduction of the weight of a man by 30 per cent may lead to a reduction in his requirement of energy by 44 per cent,

a factor of conservation. Allen and Du Bois (1) commented on this fall in metabolism as affecting individuals who are under weight, for they found that twenty "normal controls," selected by Benedict and Joslin (3) for comparison with diabetic patients, proved to have an average metabolism which was 8.6 per cent less per square meter of body surface than the general average among normally nourished individuals. Allen and Du Bois also noted the great reduction of heat production in diabetic patients fasted in accordance with the Allen program of treatment. In Geyelin's diabetic patient, C. K., the original body weight was 74.1 kgm. before the onset of the disease. Calculated on the normal Du Bois standard for human nutrition of 40 calories per square meter of body surface per hour, his basal metabolism would have been 1920 calories daily. After having been the subject of severe diabetes and prolonged undernutrition this individual, when he again oxidized glucose, manifested a basal metabolism of only 1032 calories daily, or 25.4 calories per square meter of body surface per hour. The reduction in body weight had been 43 per cent and in total heat production 46 per cent below the original normal level.

Next in historical sequence come the important experiments of Zuntz and Loewy (57), (58) who for many years had been masters in the craft of metabolism workers. The metabolism records of Zuntz cover a period of 29 years and may be thus epitomized:

Metabolism of Zuntz

YEAR	AGE	WEIGHT	O_2 CC. PER MINUTE	CALORIES PER SQUARE METER (MEEH) PER DAY
		kgm.		
1888	41	65.2	236	804
1901	54	67.6	231	780
1903	56	67.6	228	773
1910	63	68.5	235	792
1916	69	60.6	198	709
1917	70	59.4	198	723

There was no influence of age upon the heat production up to the sixty-third year of Zuntz's life. Zuntz at the age of 65 was able to sit up all night and personally supervise a metabolism experiment which lasted 24 hours. He was then still physically young. Between 1888 and 1910 the metabolism of Zuntz had varied between 16.4 and 17.3 small calories per minute and kilogram of body weight. The reduction in body weight due to the undernutrition of the war not only

reduced the heat production per square meter of body surface but also the calories produced per kilogram and minute fell to 15.65 in 1916 and 15.9 in 1917.

The experiments upon Loewy tell in part the same story. The necessitous times reduced his body weight from 65 kgm. in 1914 to 57 kgm. in 1916, a loss of 12 per cent. Whereas before the war he produced 726 calories per square meter of body surface and a total of 1429 calories daily, or 22.9 calories per kilogram per day, in 1916 the requirements of his basal metabolism were 631 calories per square meter, a total of 1169 calories or 20.5 calories per kilogram. But in 1917 Loewy's weight had fallen to 51 kgm., a total loss of body weight amounting to 22 per cent since the beginning of the war. In July, 1917, the urinary nitrogen excretion had risen to 17 grams when there were only 7 to 8 grams of protein nitrogen and between 1500 to 1800 calories in the dietary (see p. 530). A higher energy metabolism was the result of the higher protein metabolism, as is always to be anticipated under such conditions. The emaciated body of Loewy under the circumstances produced on July 23, 1917, as its basal metabolism, 758 calories per square meter of surface (Meeh), 25.6 calories per kilogram, and a total of 1307 calories for the day. Zuntz and Loewy compare this result with the finding Zuntz (56) had previously made upon an undernourished dog the energy requirement of which was increased during the later stages of undernutrition, as appears from the following:

	WEIGHT	CALORIES PER SQUARE METER
	kgm.	
Start	10.0	931
Eleventh month	4.98	631
Twelfth month	4.1	921

Presumably, toward the end the body fat failed to supply the requisite energy, and body protein was the sole remaining resource to make up the deficit of energy in the dietary.

It is to be hoped that an experiment like that upon Loewy will not be repeated in the near future, but though it stands by itself, it must be accepted as representing one of the probable contingencies in extreme emaciation.

The work of Benedict (4) and his associates concerned itself with determining the basal metabolism of the healthy young men whose weight was being reduced by administering a diet containing some good animal protein, but decidedly deficient in caloric value (see p. 528).

The results upon the eleven young men composing squad A may be thus summarized:

	DURING NORMAL DIET (3000 CALORIES) SEPTEMBER 29-30	END OF PERIOD WITH REDUCED DIET JANUARY 26-27	PER CENT REDUCTION
Basal metabolism in calories (Table 128)	1686.0	1367.0	19.0
Calories per kilogram (Table 132)	25.2	22.3	11.5
Calories per square meter body surface	940.0	788.0	16.2
Body weight in kilograms*	67.0	61.3	8.5

*Calculated from above data.

During the period of reduction the diets usually contained 2000 and later 1500 available calories. The Sunday and holiday periods were uncontrolled.

Of greater import is the result of the sudden reduction in the dietary of squad B. An intake of food stated to have contained 4000 calories daily per man was reduced to one containing 1375 net available calories per man per day, and this lowered dietary was continued for a period of 3 weeks.

While partaking of the normal diet squad B on four different occasions showed measurements of basal metabolism amounting to 40.5, 40.7, 40.3 and 39.6 calories hourly per square meter of body surface (Du Bois formula). The last and most important determination upon this diet showed a value of only 36.8 calories. Benedict writes of this determination, "The possible factors of fatigue and depth of sleep thus entered into this experiment as in no other one in this series."

If one be permitted to assume that the true normal basal values for these men are averages of the two determinations 40.3 and 39.6 calories per square meter, and 1.08 and 1.06 calories per kilogram of body weight, then one may perhaps be allowed the liberty of rearranging Benedict's table 34 and add to it the analysis presented on page 529 of this review. Such a rearrangement gives the following information:

	DURING NORMAL DIET	END OF PERIOD OF 1375 CALORIES	PER CENT REDUCTION
Basal metabolism in calories	1745.0	1293.0	32.0
Calories per kilogram	25.7	20.4	20.0
Calories per square meter body surface	872.0	647.0	27.0
Body weight in kilograms	67.9	63.4	6.5
Body nitrogen in grams	2037.0	1972.0	3.2

This table shows that the loss of a paltry 65 grams of body nitrogen bears no relationship to the enormous reduction in basal metabolism which follows the ingestion of a diet containing an inadequate content of calories. So not only is there a mechanism of nitrogen minimum, protecting life from destruction (see p. 527), but here also appears a biological adaptation to a lowered energy intake, preventing the exhaustion of the reserve of body fat.

One can compare the results obtained here with the results calculated by Lusk (37) regarding the man who fasted 31 days in Benedict's laboratory:

	BENEDICT'S FASTING MAN	BENEDICT'S SQUAD B
Percentage reduction in basal metabolism	29	32
Loss of body nitrogen, grams	277	65
Percentage loss of body nitrogen	16	3

It is quite extraordinary that the ingestion of a dietary deficient in calories, extending over 3 weeks, should bring down the basal metabolism of well-nourished young men to the same extent as fasting might have been expected to accomplish. A minimal metabolic rate, which is two-thirds that of the normal basal metabolism, seems to be easy to establish and affords another of those striking "factors of safety" of which Meltzer has so cogently written. Whether the reduction be due to a disturbance in the glands of internal secretion, to a diminished secretion of thyroxin in the absence of adequate protein and calories in the diet, for example, is a field for speculation and investigation.

The effects of a normal diet after undernutrition. No satisfactory experiments regarding the effect of a sufficient diet following one which induced undernutrition have ever been recorded in man.

	WEIGHT	CALORIES PER HOUR	R. Q.
	kgm.		
Basal metabolism, normal nutrition	9.25	15.5	0.80
Fifteenth fasting day	7.45	13.0	0.73
Second day of food containing 14.3 cals. per hour.	7.6	12.6	0.80
Day after food containing 28.6 cals. per hour	7.9	13.0	0.93
After 8 days of food containing 28.6 calories per hour	8.0	13.9	0.88

Anderson and Lusk (2) made the above observations upon the influence of a normal maintenance diet upon the basal metabolism of

a dog before and after fasting. The food was given at one time 18 hours before the metabolism was determined.

Evidently the condition of the body and not a large influx of food on the day previous determines the height of the basal metabolism.

The production of mechanical work during undernutrition. There is no doubt that the well-nourished individual feels a zest for his work, while the under-nourished tries to avoid all work. Walking gives no pleasure to an underfed seamstress nor golf to a half-starved professor.

Important results have been obtained experimentally by Jansen (27) upon men who accomplished heavy work when partaking of an insufficient diet. Three subjects abstained from muscular work for 3 days and then they walked together over level ground distances of 18, 20, and 25 kilometers (11, 12.5, 16 miles) on 3 successive days. This was accomplished in a driving snowstorm, while underfoot there was mud and melting snow, so that tramping was exceptionally difficult and wearisome. The diet remained the same throughout the experiment and contained 60 grams of protein and 1628 calories, the official Munich ration of the time (see p. 528). The labor of making such a walk would not have been great under ordinary circumstances, and yet the subjects returned home each day over-fatigued and exhausted. Each of the subjects on one occasion, was forced to come home by tramcar during the return journey, so great was the fatigue experienced. One of them (Ebert) on his return home fell into a state of prostration through weakness. The skin was pallid, respiration shallow and quickened, pulse small and slow, temperature subnormal, profuse sweating from the whole body surface; there was no acetone in the urine. Another of the subjects gave indications of the same symptoms on the second day. Apathy and psychic depression were present in all three men during the evenings of these days of exertion. The experiments present two different findings as far as protein metabolism is concerned. In one person the protein metabolism was not increased as the result of muscular work. In the other two persons the habitual nitrogen deficit increased about one gram daily above the deficit induced by the low caloric diet. This corresponds to an increase of about 10 per cent in the total protein metabolism. These results may thus be summarized in the accompanying table.

The average weight of the three men at the time was 57 kgm. A complete explanation of the increase in protein metabolism due to work is not possible.

SUBJECT	PERIOD	FOOD		EXCRETA N	BODY N
		Calories	N		
Ebert	Rest	1630	9.61	11.83	−2.22
	Work	1628	9.54	12.70	−3.16
	Difference				−0.94
Legène	Rest	1630	9.61	11.55	−1.94
	Work	1628	9.54	10.76	−1.22
	Difference				+0.72
Beholz	Rest	1630	9.61	10.81	−1.19
	Work	1628	9.54	11.78	−2.22
	Difference				−1.03

Two of the men were subjected to respiration experiments 12 hours after the second and third days of walking. These experiments had to be carried out at so late an interval because the persons concerned were too exhausted immediately after their walks to be satisfactory subjects for experimentation. The experiments yielded surprising results, both as regards the duration of the after-effects of the exercise and the height of the metabolism. For example, the average increase in the basal metabolism of Legène was found to be 50 per cent above the normal, or an increase from 1440 calories to 2160 for 24 hours. High respiratory quotients were noted, the average being about unity. Jansen states that the explanation of this high quotient lay in the irritable condition of the subject. The subjects, who had formerly yielded themselves freely to this form of experimentation, no longer had either the will power or the physical energy requisite for accomplishing an exact experiment and fell into a state of excitement which was manifested by the increased respiratory movements. The ventilation of the lungs was abnormally increased. This would lead to an "Auspumpung" of carbonic acid from the blood which would explain the high respiratory quotient. There must have been stimuli, perhaps organic acids, circulating in the blood, which acted to stimulate the respiratory center.

This clear-cut presentation of disaster following severe labor during undernutrition was presented by Gowland Hopkins to Chittenden and me at a private meeting held in the rooms of the Royal Society in London, March, 1918, as an unanswerable argument against the reduction of the importation of bread for the people of the United Kingdom.

Iltzhöfer (25) explains the great increase in pulmonary ventilation following muscular exertion when taking a low diet containing 1630 calories as being due to an increased susceptibility of the respiratory center to hydrogen ions.

Iltzhöfer (26) has recently published the details of the respiration experiments upon the medical students investigated by Jansen, and shows that another person, when partaking of a normal diet in 1918, gave no indication of increased metabolism following the accomplishment of mechanical work similar in amount to that done by the medical students. An interesting point is brought out by Loewy (58), who found that in his exhausted condition induced by undernutrition (see p. 530), there was an increased production of calories in his body for accomplishing a unit of mechanical work when he walked on a moving platform set at an incline of 22 per cent. For example, in one experiment, after 9 minutes of climbing, 6.5 calories were required to raise 1 kgm. of his body weight 1 meter high, whereas after 35 minutes, 8.6 calories were required to do the same amount of work, an increase of 32 per cent. No similar increase would have been observed in a normally nourished individual. Loewy, who was 57 years old, remarks: "It is not astonishing that an older man, exhausted by undernutrition, should quickly experience an increase in metabolism per unit of muscle work. It is the expression of diminished muscle power or of previous overexertion."

It is evident from these experiments that the human body has no means of economizing energy for the production of work when work is done after emaciation and during undernutrition.

In the case of squad B, investigated by Benedict, the individual men were caused to walk on a treadmill at the rate of 2.6 miles per hour before and after their reduction in weight by a diet of 1375 calories daily. The increase in metabolism involved in moving one kilogram of body weight in a horizontal direction was tested. The results were very variable. Of eleven subjects tested after the 3 week period of undernutrition, four showed an increase in metabolism per horizontal kilogrammeter of body movement, one no change, and six a decrease from the level found when the men were living on a normal diet. Averaging the whole material, Benedict finds that the men after reduction can propel a kilogram of body weight one meter horizontally at an average expenditure of energy which is less by 6 per cent than was necessary to effect the same amount of work in the state of normal nutrition.

This does not accord with the results obtained by Joffe, Poulton and Ryffel (28), who compared the efficiency of an under-nourished individual, the basal metabolism of whom was only 26.6 calories per square meter of body surface per hour (Du Bois formula) instead of the normal of 40 calories, with the efficiency of a normally nourished person. The individuals walked at rates varying between 3 to 5 miles an hour. It was concluded that when the individual is not fatigued, prolonged undernutrition causes no alteration in the efficiency with which musular work is carried out. The energy equivalent necessary to propel 1 kgm. 1 meter horizontally is the same in the state of undernutrition as in the state of normal nutrition. This accords with the experiments of Anderson and Lusk on the dog (see p. 542)

No experiments have been made to test the capacity of endurance in such men as Benedict investigated. It would be interesting to have men ride stationary bicycle ergometers until they were exhausted, *a*, before reduction, *b*, after reduction on an insufficient diet, *c*, after reduction on a sufficient diet.

The general physical reaction of the men to undernutrition Benedict described as follows:

1. Feelings of general weakness and tiredness, a condition commonly expressed in college slang as lack of "pep" or drive, when it seemed to require more energy to accomplish a given amount of work and it was necessary to urge one's self harder.

2. Weakness of the legs and accompanying unpleasant sensations of fatigue, particularly in stair-climbing.

3. Subnormal gymnasium and athletic performance, as shown by inability to continue the rapid calisthenics or to do the heavy apparatus work for the prescribed time and with the usual subjective satisfaction and generally to produce effectively sudden bursts of energy.

I have been informed by one who was a constant and expert witness of the gymnasium performances of these men that they could be readily differentiated from their fellows by their distinct lack of physical power. After the restricted diet the men ate food in enormous quantities and rapidly regained their original weights. No experiments upon their physical power immediately upon return to an adequate diet were made. It would be very important to determine if, given adequate food fuel to sustain prolonged muscular effort, men who had been moderately reduced in weight as were these subjects of Benedict would not have been equally powerful physically after reduction as they had been prior to the period of undernutrition. Rubner (49), however,

affirms that an increase in efficiency after undernutrition is to be observed only in those who were formerly over weight.

In work upon a dog Anderson and Lusk (2) found that the quantity of energy required to accomplish a given amount of work was the same whether the dog was in the best nutritive condition or had lost 20 per cent in weight after 13 days of fasting. The dog moved horizontally on a treadmill at the rate of 3 miles (4800 meters) per hour, and when well nourished accomplished this work at the expense of an extra energy production of 0.580 kilogrammeter per kilogram of body weight transported 1 meter, whereas after 13 days of fasting an energy equivalent of 0.584 kilogrammeter was required to accomplish the same unit of work. By reduction of the body weight, therefore, it was concluded that one may economize in the quantity of basal metabolism, one may economize in the quantity of food fuel required to move the lesser body weight, but if a given amount of work is to be done it can be accomplished only at the expense of a definite quantity of energy, irrespective of the body weight. The very constant results obtained with this well-trained dog are in marked contrast with the extremely varying results obtained subsequently by Benedict (see p. 540) upon men before and after reduction of their body weights, but they are in agreement with the findings of Joffe, Poulton and Ryffel. It should be remembered that dogs are often fasted for several days before they are run in a hunt, without any evident decrease in their muscular power.

Anatomical changes within the body. It has been noted by German authorities (50) that the loss of body fat causes a considerable displacement of the anatomical position of various organs of the body. In many a loss of subserous and mesenteric fat produced conditions in which the stomach and intestines were not as firmly held in position as formerly. A greater displacement of the heart and a ptosis of the stomach, intestines, kidney, uterus and vagina were observed. Cases of rupture and intestinal obstruction were commonly reported (9). Accompanying the general atrophy in human beings caused by inanition Kreger (34) describes a great diminution in the weight of the spleen, liver, pancreas, heart, testis, thyroid and kidney, while the brain and adrenal lose little or no weight.

Chemical changes within the body. When body fat is oxidized it is often replaced in the body by the addition of water, as has been shown by Grafe (18) in cases of obesity. Schirmer (52) finds that the fatty tissue of lean people is richer in water and connective tissue than is that of fat people. The muscles of thin people also contain more water than do those of fat people.

Schirmer likewise finds that the fat derived from the muscles of corpulent people has a higher iodine number and inferentially contains more oleic acid than does the fat found in the muscles of thin people.

The chemical composition of the protein composing the muscle of a dog appears to be independent of diet, whether rice or meat be fed, or of the nutritive condition of the animal. Diesselhorst (10) found in one dog that a sample of the dog's muscle showed that the C : N ratio of the protein content (what remains after extracting with water and ether) was 1 : 3.188 during fasting and 3.185 after taking a mixed diet. One would hardly expect that the chemical constitution of living protein would change in its essential constitution, only that its quantity in the cell might vary.

The influence of external cold. All authorities are united in the belief that the undernourished organism is far more suceptible to the sensation of cold than is the well-nourished. Protein, the most costly of the food-stuffs, causes a specific stimulus which increases the heat production, and carbohydrate and fat, when absorbed in excess of the immediate requirements of the body, both cause an additional heat production. In the well-nourished body these factors are protective against the sensation of cold. In the undernourished body, not only is the heat production reduced per kilogram and per square meter of surface, but the lack of protein and of an excess of calories in the food supply reduces to a minimum the extra production of heat following the ingestion of food. The body would then naturally react to conserve its heat resources by vasoconstriction of the superficial arterioles, which would leave the skin cold and therefore the temperature receiving sense organs especially sensitive to cold.

It is quite probable, though not definitely ascertained, that the phenomenon of increased heat production in the presence of cold (the chemical regulation of body temperature) would be accentuated in the presence of undernutrition, thereby becoming an important element in the reduction of the quantity of available body fat. The outcast who has suffered from hunger and cold is not in fit condition to saw wood.

The heart and circulation. Undernutrition reduces the number of heart beats per minute. Rubner (50) states that in the emaciated there is a slowing of the heart rate to 60, 50 or even to 40 per minute. The work to be accomplished by the circulation is certainly not as great as formerly. Determan (9) concludes that this reduction of the burden upon the heart and the blood vessels must be beneficial in heart disease and especially in arteriosclerosis.

In an elaborate study by Benedict and his associates of the pulse rate of men who had been reduced by partaking of a diet containing 1375 available calories daily for 3 weeks, a considerable number of them showed pulse rates reduced from a normal average of 56 to an average of 40 beats per minute. The records were taken early in the morning when the men were still in bed. The rate is as low as was observed in war edema in Germany. Electrocardiograms of these hearts showed normal conditions. There appeared to be no change in the functional efficiency of the heart; the reduction of rate was merely an accommodation to the lessened requirements of circulation. There was the usual adaptive increase in rate when additional work was called for. The blood pressure was reduced. The average systolic pressure fell from 120 mm. to 94 mm. and the diastolic from 83 mm. to 64 mm. The pulse pressure was therefore diminished from 37 mm. to 30 mm.

The influence of sex. German writers are generally agreed that the war diet tended to produce a cessation of the menses. Rubner (50) thinks that this complex undoubtedly depends upon the great reduction in the protein content of the diet. As this latter factor approaches the nitrogen minimum or falls below it, amenorrhea sets in as a protective factor. A great reduction of body weight is not essential. Eckstein (12) says that reports of this difficulty show that sometimes as high as 6 per cent of the women concerned in an investigation might be affected, so the trouble was by no means general. The cessation of the menses lasted between 2 to 18 months.

The development of the ovum and the ability to nurse the offspring were not reduced (53). Likewise the chemical composition of the mothers' milk was unchanged (44), though its quantity might be reduced. During 1916–17 the death rate among infants was below normal because mothers in increased numbers suckled their offspring. All this confirms the biological principle of the sacrifice of the mother for the welfare of the offspring.

Many German writers, as also Benedict, report that a reduced diet diminishes the *libido sexualis* among men.

War Edema. The occurrence of edema during a famine in France following the Napoleonic wars has already been described. The same phenomenon occurred in different localities in Europe during the World War. Rössle (48) states that in Bohemia in the year 1917, 22842 cases were reported, of whom 1028 died. Nine per cent of the inhabitants of one small town were afflicted with the disease.

The condition of edema occurs after chronic inanition extending over months and years and upon a diet containing predominantly carbohydrate and little protein. Schiff (51) states that he has occasionally seen apparently well-nourished individuals with this disease. A carbohydrate diet tends to favor an accumulation of water in the tissues. The occurrence of the trouble was widespread, especially in the cities, and occurred predominantly in the early part of 1917 when turnips replaced potatoes in the dietary. The older men, 40 to 55 years old, were especially affected, younger people and women much less. There was a swelling of legs, arms, and sometimes of other parts, but no pathological changes in kidney, heart, or liver, nor was there any other severe organic lesion. There was bodily weakness, slow pulse (40 to 48), a reduction in the volume of the blood, polyuria (3 to 4 liters), blood hydremia and sometimes nervous symptoms. Rest in bed and better food—more fat, milk, meat and bread—usually effected a cure. The mortality rate was not high.

Rubner (50) has never noticed this condition in fasting dogs, and concludes that the acute road of starvation yields a sufficient amount of protein metabolism, and this he considers to be the essential factor in preventing the edema. The functional disturbances may be very severe and often do not disappear with the regression of the edema, while weakness and emaciation, slow pulse, and frequent urination may persist for a long time after again taking a normal diet. Even the best treatment does not always prevent a fatal outcome, though autopsy may show no organic lesion. There is in general a regression of the disturbance when fresh foods are obtainable from a new harvest.

Those who have been cured by dieting are susceptible to a recurrence of the disease if the poor diet is again taken.

Knack and Neumann (30) found a reduced quantity of lipoids in the blood of patients suffering from edema. They think that this reduction of lipoids may cause damage to the capillaries and to the cell walls, thus increasing the permeability of both. After administering carbohydrate alone in the form of turnips, or excess of water alone, to a patient who had recovered from edema, there was no recurrence of the difficulty, but when both were administered together edema followed.

Harden and Zilva (20) gave to a monkey 250 to 300 grams of polished rice daily, with a yeast preparation to furnish the water soluble vitamine, prepared lemon juice to furnish the antiscorbutic vitamine, and a salt mixture. The experiment began on May 16, 1918. A decline

in body weight began the end of January. Edema developed on February 27, 1919, 289 days after commencing the experiment. The edema persisted and grew gradually worse, a severe diarrhea set in, and the animal was chloroformed on account of its suffering.

Falta and Quittner (13) believe that the edema is due to the large amount of chloride ingested in the food and is analogous to diabetic edema following the ingestion of sodium bicarbonate together with a diet rich in salt. The day's urine, which is always free from albumin, may contain 40 to 45 grams of sodium chloride.

In some excellent studies upon rats Kohman (31) was able to produce edema in them by giving a diet composed largely of carrots with carrots as the only source of protein. Fats or fat or water-soluble vitamines did not prevent the occurrence of the edema in these rats living on a low protein diet. The salt content of the diet had no noticeable effect. A large water intake favored the development of the trouble. Control rats received casein as an addition to the diet, and remained in good health. Hence, the carrots did not contain "toxic" substances. This research confirms the opinion of Rubner that a diet low in protein produces edema.

Maver (40), reviewing the literature of nutritional edema, finds no indication that a lack of vitamines is concerned in its production.

Rubner (50) notes that *polyuria* was extensively observed in 1917 and is to be explained by the enormous water content of the diet for on account of a lack of fat the food intake consisted of bread, turnips, vegetables, potatoes and soup preparations. It was noticeable that urinary secretion took place, especially during the night hours, and bed-wetting was of frequent occurrence, even in adults. This was due to a delayed absorption of food, a more profound sleep in weakened individuals, to the absense of urea and the purins, and of tea and coffee as diuretic agents.

Metabolism of atrophic children. The same problems of energy production are met with in undernourished children as in the cases of adults. Howland (23), (24) investigated the metabolism of two normal infants (I and II); also the metabolism of a boy (III) 6 months old who was in a condition of extreme malnutrition, was literally skin and bones, with no fat and very little musculature; and finally the metabolism of an 8 year old girl (IV) emaciated to a most extreme degree and almost devoid of musculature. She had suffered from cerebrospinal meningitis 6½ years before.

The energy metabolism of these children may thus be given:

Heat production in normal and undernourished children

	CONDITION	AGE	WEIGHT	CALORIES IN 24 HOURS				PER KILOGRAM
				Indirect	Direct	Per square meter surface		
						Indirect	Direct	
			kgm.					
Child I.....	Normal	3 mos.	4.65	340	333	1084	1046	71.3
Child II.....	Normal	7 mos.	4.32	358		1270		83.0
Child III.....	Malnutrition	6 mos.	3.05	188	191	868	886	62.0
Child IV.....	Atrophic	8 yrs.	6.60	293		809		44.4

The children were all nourished with milk, and the determinations were made when they were asleep after food ingestion. Howland's formula (24) for determining the surface area of children was employed. Using this formula, the results are usually not far from those obtained by using that of Lissauer.

It appears from the above table that the metabolism of atrophic children is less per kilogram of body substance and per square meter of surface than in normal children.

It is to be greatly regretted that no work similar to this has yet been published concerning the metabolism of undernourished children in Vienna.

Von Pirquet's (47) system of nutrition, which need not here be analyzed, seems to have given excellent practical results in the nutrition of the underfed Viennese children. Concerning this system von Leersum concludes, "plus que ça change, plus c'est la même chose." Fleming (14) states that only when children are one-third under weight for their ages is the metabolism abnormally decreased.

Xerophthalmia. McCollum and Davis (38) and, independently and almost at the same time, Osborne and Mendel (45) found that if rats were reared upon a synthetic diet which included lard or a vegetable fat the animals, after about 2 months, ceased to grow and became afflicted with an inflammation of the eyes, xerophthalmia. Osborne and Mendel (46) noted the great efficacy of cod liver oil as a cure for this condition. Xerophthalmia has been more common in Denmark than elsewhere, probably because the poor there eat vegetable margarine and export Danish butter. In 1917, during the submarine blockade, the prevailing doctrine in Denmark was that of Hindhede to the effect that fat was a dispensable foodstuff, an error also cham-

pioned by von Pirquet (47A). There was then no knowledge in Denmark of the American work. Bloch (5) (6) describes how the Danish children grew to be weaklings, without appetite, under height and under weight for their ages, and they developed xerophthalmia. These conditions were cured by rationing butter and selling it to the poor at low prices. Administration of full milk and cod liver oil were also effective. Ten grams of cod liver oil, given twice daily, cured the xerophthalmia in 8 days except in cases in which its administration had been too long delayed to save the eyesight.

One can hardly cite a more clear-cut example of the benefits conferred upon a people from knowledge of experimental biological science.

It is not within the scope of this review to deal with the deficiency diseases, scurvy, beri-beri, pellagra and rickets, concerning each one of which volumes have already been written, and each one of which is worthy of separate consideration.

Undernutrition and the incidence of disease. With the loss in weight it was particularly noted in Germany that there was an increased frequency of tuberculosis until, at the end of the war, the death rate from this disease had doubled or had reached the height which it had formerly attained before modern control over its spread has been instituted. More new cases were also enumerated. Young children were more susceptible to it than formerly. The increased susceptibility to cold likewise increased the number of cases of pulmonary infections. There was a great loss by death of people over 60 years old. Bodily weakness especially threatens people of old age, who may live for many years when amply nourished, but when undernourished, succumb to an ordinarily unimportant bronchitis, catarrh of the stomach, or to an acute infection (9). Recovery after surgical operations was also more difficult. On the contrary, war nutrition, by diminishing the intake of protein and preventing over-nutrition, was beneficial to many diabetic patients (43). The reduction in the quantity of alcohol taken was of benefit in all countries. In general, the gastro-intestinal tract showed itself capable of adaptation to the war diet to a very high degree (9).

The prevention of famine. From what has preceded it is evident that sufficient food is essential for the physical, mental and moral welfare of a nation, and it therefore follows that human intelligence should be used for the prevention of famine. The doctrines of T. B. Wood (55) became the recognized English agricultural policy during the war. Gruber (19) has outlined a similar policy for adoption by the German people in the light of their situation in 1920. The reasoning is funda-

mentally sound. He begins by unrolling a hopeless picture of the food situation. As the possibilities of emigration are limited, twenty millions Germans are condemned to die unless they are able to help themselves. People in their position cannot speak of "panis et circenses" but of "panis et labor." The only outcome possible is to nourish themselves from their own land and render themselves independent of foreign imports. Notwithstandig the dark prospect, Gruber believes it possible to maintain nourishment from home produce if there be no extravagance and especially if the protein intake contain only a small quantity of meat. The ox is an irrational utilizer of fodder; if too many cattle are maintained an irreplaceable quantity of fodder is wasted. Agriculture must react to accord with this. The population needs 2600 calories per person per day, or for 60,000,000 people 56 billion calories per annum. Notwithstanding the loss of agricultural districts, 171 billion calories can be produced as food for men and beasts. Of this, 26 billion are needed for horses, leaving 145 billion over for man and for edible animals. Because of the poor utilization of fodder by animals, not more than 29 per cent of the food of man should consist of milk, meat and eggs (which the fodder available could supply), whereas 71 per cent should come from vegetables. It is necessary for agriculture to appreciate its high patriotic obligation not to increase the number of cattle nor to neglect the tilled area. Of course, this is not to be accomplished by force. It must be done by explaining the situation. Gruber protests against the brewing of strong beer and against the export of native grain. The nutrition question depends upon the sense of responsibility of each individual, producer and consumer alike. The problem is not only psychical but a matter of habit and of will power. "The German people holds the fate of Europe in its hand. With starvation, anarchy will come; anarchy in Germany would mean the end of European culture."

Hindhede (21) writes: "The (German) people must first have bread, potatoes and cabbage in sufficient quantity and then some milk. Meat is the last requirement to be met. If the people must wait until the pigs and cattle have sufficient food, they will die of starvation one year before they can get an abundance of meat."

During the last year of the war E. H. Starling said vehemently in England: "We will not ration bread." The necessary calories were thereby assured. And Herbert Hoover has written, "The wheat loaf has ascended in the imagination of enormous populations as the positive symbol of national survival."

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ADSORPTION

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The subject of adsorption is too large and has too many physiological ramifications to be treated in its entirety in twenty-five pages. It seemed to me wiser, therefore, to confine this review to the fundamental principles, concerning which there are many erroneous conceptions and much confusion, together with two or three only of the physiological applications.

In a system consisting of two or more phases, and being therefore heterogeneous, it is often observed that the concentration of any substance is either greater or less at the surface of contact of the phases than it is in those phases themselves. This difference of concentration at the phase boundary is what is known as adsorption. If the concentration of the substance is greater at the surface of contact than it is in either phase, it is called *positive adsorption;* and if it is less, *negative adsorption.* The word *adsorption* comes from two Latin words: *ad,* meaning *to;* and *sorbēre,* to drink up. By *ab*sorption is meant a drinking up with the substance which is drunk up distributed throughout the drinking substance. The use of the prefix *ad,* instead of *ab,* has reference to the fact that the substance drunk up adheres to the surface and does not penetrate the adsorbent. For example, a typical case of *ab*sorption is that of carbon dioxide by alkali. In this case the gas is distributed through the liquid; all cases of solution are cases of absorption. On the other hand the condensation of water vapor on a wire net or other surface is a case of *ad*sorption; the water remains at the surface.

The distinction between these processes was not at first clearly recognized, and the early writers speak of both adsorption and absorption under the name of absorption. Thus van Bemmelen (72), one of the most important writers on the subject, defines absorption as follows:

> In all those cases in which there occurs an absorption of gases, of fluid substances, or of substances from solution (acids, bases, salts, dyes, etc.) in inorganic tissues, as in hydrogels (alcohol gels, acetic acid gels, etc.); in animal or plant

tissues; in porous amorphous substances (such as charcoal, etc.); and other amorphous substances, such as kaolin, etc.; (and I would add also all the amorphous complexes which occur in colloidal precipitates, such as those from sulphur, tellurium, selenium and so on; and also the complexes which are formed when colloidal precipitates carry down with them other substances in solution which are very hard to wash out)—; in all of these cases, I have called the compounds "absorption compounds" in order to distinguish them from chemical compounds which are formed with simple equivalent proportions, and which can be obtained in a crystalline form.

It was E. Du Bois Reymond who proposed to call surface condensations adsorptions, in distinction from absorptions, and that has become the general practice.

To make clearer what is meant by adsorption, I may cite a typical case which is familar to all and which is on so large a scale that the details of the process may be seen. Whenever we put on clothing, we adsorb the clothes. We and our environment are part of a great system. Any change of the environment produces a change in us, and any change in us produces some change in the environment. In this way we and the environment make what is known as a system, which consists of two constitutents or phases, one of these being ourselves. As it has two phases or physically distinct parts, the system is heterogeneous. Every morning when we dress, clothing which has been distributed through our environment, dispersed in the surrounding phase in other words, concentrates at the surface of our bodies; or speaking technically, it concentrates at the interphase boundary of the system, so that the concentration of clothing at that boundary becomes greater than in the room about us. This is a process of positive adsorption. And at night the process is reversed, the concentration of clothing in the room becoming greater than at the surface of the body, the clothing passes out of the interphase, and we have then a case of negative adsorption. And we might go on, if we wished, with this treating of the wearing of clothes as a process of adsorption, express it mathematically in a curve or isotherm, showing how the quantity adsorbed is a function of the amount in the room; how it proceeds usually to an equilibrium; how it is greater at low than at high temperatures; that it is reversible and not accompanied by any chemical change in the clothes; that it is specific in that certain kinds of clothes are adsorbed with greater avidity than others; that certain adsorbents (people) adsorb better than others; and finally we could prove that the clothing moved into the surface film in virtue of the second law of thermodynamics, and because of the thermodynamic potential in consonance

with the principle of Willard Gibbs. In other words dressing is in every respect a typical case of adsorption, and if we wished to go farther we could actually prove, at least as well and to just the same degree as similar things are proved for protozoa and other living things so minute that we cannot easily see just what is happening, that the wearing of clothes is a surface tension phenomenon, and has a purely mechanical explanation. Human behavior, in the wearing of clothes, would thus be explained to the satisfaction of the mechanistic philospher, and in the same manner as the wearing of mineral clothing, called shells, by protozoa has been explained. But the limits of this article are too short to permit of this demonstration, illuminating though it would be, and the case of dressing is here brought forward simply to illustrate what is the essential characteristic of adsorption, namely, a difference of concentration of some substance at the boundary of two phases, from its concentration in the phases.

Simple as the matter appears in its broad aspects, it is probable that no subject is more difficult for the ordinary reader than that of adsorption; and although this is perhaps a rash statement when the confusion in so many fields is recalled, it is certain, I believe, that in no part of the field of physiology are conceptions so foggy, so confused, and often so erroneous, as in this field. This confusion is due to several things. In the first place it is due in large measure to the mathematical treatment which the subject has usually received. Adsorption has usually been treated as if it were part of the very difficult to understand phenomena of surface tension. The mathematics of surface tension as developed by Laplace have been applied to it. Or it is treated solely from the point of view of thermodynamics, that is, of energetics, as this has been developed and applied to surface tension by Willard Gibbs, in one of the most profound and difficult papers of the whole of physical chemistry. For example, Macallum (32) and Freundlich (11) consider it wholly from the standpoint of surface tension and thermodynamics. This has confused most readers, since mathematics and formulas are but a kind of shorthand which is not understood by most, and accordingly this treatment, while it makes possible the statement of relations and their explanations in a few symbols to those who understand the symbols, adds to the difficulty of those who do not. And in another way this manner of treatment has led to great confusion of thought and concealment of real relations. I will now explain why this has been the case.

It will be seen from the definition of adsorption which has been given

that it says nothing concerning the nature of the forces which bring about the difference in concentration at the surface of the phase. Adsorption is simply a name descriptive of a result; the means by which the result is obtained is a matter of indifference. It is just as if we were treating of the property of bodies of being spherical. We can speak of the sphericity of the earth, of a drop of water or of a toy balloon. Each of these shows the property of sphericity, which is readily comprehended. And we might go on and extend this to all the bodies in nature which are more or less spherical and speak of negative and positive sphericity. But when we speak of sphericity we say nothing at all, and imply nothing at all, of the nature of the forces by which that spherical form is attained. Let us suppose now that some one studied the sphericity of a drop of water and found it due to surface tension. He might then treat the sphericity of the earth in the same way from the point of view of energetics and he might even extend his treatment to the sphericity of the toy balloon. He might conclude that all three were but cases of surface tension. Sphericity would thus come to be tied to the idea of surface tension and might be made as difficult to understand as the latter subject. He would be in gross error of course, since the sphericity of the earth has nothing to do with surface tension. But this is just what has happened in the case of adsorption. Among the earliest cases of adsorption studied were those which occur at the surface of a solution, and it was this phenomenon which was worked out mathematically in its general principles by Gibbs. Consequently the attempt is usually made to refer all cases of concentration changes at the boundary of two phases to surface tension. This has led in the minds of many to the wholly erroneous conclusion that all cases of adsorption are due to surface tension and are not due to chemical or other forces. And this tendency has been strengthened or confirmed by the present uncertainty as to the nature of chemical force on the one hand and cohesional force on the other. Consequently for all these reasons it has come to pass, as will be seen in the quotation from van Bemmelen, that the word adsorption has come to have a double meaning: *a*, the correct meaning simply descriptive of the change of concentration at the boundary of the phases; and *b*, an incorrect conclusion that all such concentration changes are produced by surface tension or some other equally obscure physical force, and that they are not due to chemical force.

Another great source of confusion of thought has been the thermodynamic treatment the subject has received. In this method of treat-

ment we disregard entirely all the material aspects of the nature of the process which brings about the result, and we deal wholly with the changes in free energy. It is a matter of indifference to this method of treatment whether the energy is of one kind or another. A start is made with the very general principle embodied in the second law of thermodynamics, that all spontaneous events in nature occur in the direction of reducing the intensity factor of the free energy. This is simply another way of saying in general and precise language that water tends to run down hill rather than up; that electricity flows from a higher pressure to a lower; that salts diffuse from the point where they are more concentrated to the point where they are less; that a gas under pressure will, if allowed to do so, flow into a container in which it is at a lower pressure; that heat flows from hot bodies to cooler. This general principle holds everywhere. It has a particular value, it may be said parenthetically, for biology, for it is in virtue of it that events in nature tend to be self limited; that organisms tend to surround themselves with membranes which protect them from environmental changes, a result which is at the very foundation of the creation of an individual; that they appear to struggle against the environment so as to preserve their balance; that the need produces that which satisfies the need, as Hering put it. In fact, it is this general principle which in living nature finds its expression in that great, and finally successful, struggle against the environment which we call evolution and made of it in its physical aspects one great struggle for freedom from the environment; and in its psychical aspects reveals itself in the phenomena of the will, the aspirations of the human mind and the longing for final freedom and immortality.

Now as has been said it is a matter of indifference to this general principle of energetics what may be the particular form of energy concerned. If a substance concentrates at the interphase boundary it may always, in all cases, even for example in the wearing of clothes, be shown that this takes place in virtue of this general principle. But it will make no difference to the applicability of the principle whether the actual form of that energy is kinetic or potential; whether it is chemical, surface tension energy, cohesional, gravitational, electrical, magnetic or human, as in the wearing of clothes. And nothing whatever can be assumed as to the nature of the processes because the energy relations are satisfied.

It is the failure to recognize this fundamental fact which has led, in my opinion, to much of the confusion on this subject. Several

authors have clearly pointed this out, among them Bayliss (3), in his *Principles of General Physiology*, but they sometimes continue, as he does, to use the language and conclusions of those who have not perceived this essential fact, and they accordingly mislead their readers. We cannot for a moment agree, for example, with Bayliss when he says (p. 55): "Given the diminution of surface energy, the adsorption process is thermodynamically bound to take place, and any other explanation of the phenomenon is superfluous." It is evident that much may be written in explanation of how clothes came to be worn besides the statement that this is caused by the thermodynamic potential. This tells us really nothing at all of just what we wish to know and must know if we are to comprehend the process. It aids very little to say that a substance collects at the surface of a colloid particle because that is thermodynamically bound to happen. Some other explanation is far from being superfluous; for this tells us nothing at all of the mechanism of the process.

The uncertainty in the implications of the word "adsorption" is apparent if the treatment of the subject by Bancroft (2) in his recently published, valuable and stimulating book on *Applied Colloid Chemistry* is contrasted with that of Taylor (66), for example. Bancroft considers a vast variety of phenomena under this head, such as dyeing, tanning, gelation, painting, the floatation of ores, etc. He treats the process objectively and does not attempt to explain it except by the application of general principles of thermodynamics. He is indifferent whether the forces which produce the result are chemical, physical, electrical or what not. Nevertheless he treats these processes as if they were of one kind and in some way different from other chemical compounds, and he thus confuses the reader, who does not see clearly that a great variety of results produced in quite different ways, is included. On the other hand Taylor (66), after defining adsorption as it has been defined at the outset of this paper, proceeds to distinguish between true and pseudo-adsorptions. Those which are clearly due to chemical force he would throw out and call pseudo-adsorptions, confining the word only to physical unions produced in some obscure way by surface tension, as in the condensation of gases on solids. Most dyeing is therefore excluded by him. His treatment is not consistent with his definition. Bechold (4) also falls into a similar error. He says: "Adsorption is a phenomenon which is determined by the diminution of surface tension of the solvent by the dissolved substance, at the boundary surface between solvent and

adsorbent." "From all which we have adduced, adsorption appears as a physical phenomenon, in which no chemical relations between adsorbing and adsorbed substance play any part. We will therefore designate this purely physical phenomenon with Wo. Ostwald as mechanical adsorption." He uses the term adsorption throughout as implying a physical rather than a chemical union. A striking instance of this confusion of the phenomenon with its cause is given by Wo. Ostwald (52) in his attempt to prove that the union between oxygen and hemoglobin, i.e., the taking up of oxygen by the blood, is a case of adsorption in distinction from a chemical union. He bases this purely on the fact that the variation of the amount of oxygen adsorbed with a variation of pressure, at any given temperature, follows what is known as the adsorption isotherm, that is, it follows the course taken by other easily dissociable unions which are in equilibrium. He is confused into thinking that all adsorptions are of the same kind and that they are physical rather than chemical. As a matter of fact the taking up of oxygen by hemoglobin is actually an adsorption, since the size of the hemoglobin particles is so large, they being colloidal, that the solution is diphasic; but the forces holding the oxygen to the hemoglobin are not physical, they are chemical, as has been clearly proven by the crystal form, spectrum, stoichiometrical relationship and so on.

Another striking instance in which the word is used as if it implied something as to the nature of the forces involved is given by Traube (69). For him nearly everything is an adsorption. All the action of drugs is due to adsorption; sodium adsorbs chlorine to make sodium chloride. By adsorption he means a purely physical process in distinction from chemical. But as he perceives at once that this is getting him into difficulties, he goes on to hedge with the remark that there is no difference between physical and chemical unions, thus giving away his whole argument. He attacks vigorously those who think that chemical constitution and chemical properties play any part in the pharmacological action of drugs. Pharmacology, he thinks, must be entirely rewritten from the adsorption point of view. The neutralization of a toxin by an antitoxin is an adsorption, not a chemical union. He himself has attacked the anesthetics, alkaloids, etc., from this point of view, and armed with his stalagmometer, like Diogenes with his lantern, he goes about hunting in vain for a drug which acts in any honest, chemical way. Whatever may be the outcome of our studies of the nature of drug action, I think this may be cited as simply an obvious case where enthusiasm and the false idea that all adsorptions are due

to physical, in distinction to chemical forces, and in fact to surface tension, has confused the thought and betrayed an able and talented investigator into an entirely untenable and false position.

Finally a great part of the confusion is due I believe to Freundlich's book on *Capillary Chemistry* (11). Able, interesting, stimulating as that book is, it has produced general confusion for the reason that it has treated all the phenomena of adsorption under one aspect, namely that of thermodynamics as applied to surface tension. Surface tension is but one of the indirect results of the force of cohesion. If surface tension is extended to cover the energy potential at all surfaces, solid, and gaseous as well as liquid, it is better to call it the free energy of cohesion. It is confusing to give to the general phenomenon the specific name of the resulting effects at the surface of liquids. If, for example, one reads that the condensation of a gas on the surface of a solid is brought about by surface tension, one is puzzled and confused, for he cannot apply to a solid the changes of the mobile surface of a liquid. And as a matter of fact the condensation is not due to surface tension at all. But it is due to cohesion. So why not say so? To say that gas molecules adhere to the surface of solids, when they strike them, because of the force of cohesion, brings the phenomenon at once into the experience of everyone and enables him to form a clear idea of it. Cohesion is one of the forces of attraction of nature; surface tension is not.

So much by way of introduction. Adsorption is a name descriptive of a physical (or chemical) phenomenon. It says and implies nothing as to the cause or causes which produce the phenomenon described by it. Those causes may be chemical, cohesional, electrical, magnetic, gravitational or other forces, and each case must be investigated by itself to discover just what force is concerned. And finally it has not as yet become the general fashion to apply the term adsorption to unions in which both of the constituents are smaller than 1×10^{-7} cm. in diameter. One of them must be at least this large so that it may be called colloidal. A considerable portion of the field of chemistry has accordingly until now escaped annexation by the province of adsorption.

The great importance of adsorption in biology arises from the fact that there is an enormous amount of surface bounding the different phases in living matter. There is not only the external surface in which shells are deposited, or membranes formed, carbohydrate, mineral, protein or fatty matter accumulated (70); but there are

also within the protoplasm itself vast surfaces of the colloidal particles, granules, membranes, such as those of the nucleus, nucleolus, chromosomes, chondriosomes, mitochondria, filaments, cilia, fibrils, and so on, at the surface of all of which, substances may concentrate or which they may avoid (32). We must therefore study the properties of surfaces if we are to understand these phenomena of the cell. Therefrom arises the interest of physiologists in this subject. It is the organization of the cell, that fundamental thing; its chemical and physical differentiation, which we are seeking to understand. Living matter is largely composed of colloidal substances, and colloidal chemistry, as Bechold (4) has put it, is sailing under the flag, I might almost say the black flag, of adsorption. It is in fact a piratical ship with a piratical crew seeking to make all our old ideas walk the plank.

Let us therefore examine the phenomena of adsorption in the inorganic world and try to get thereby a clear idea of the forces with which we have to deal in living matter.

THE ADSORPTION OF GASES AND VAPORS BY SOLIDS. All solids have the property, although to very different degrees, of condensing on their surfaces gases, vapors and liquids. What is the nature of this process? Is the gas held at the surface by chemical forces or by cohesional; or is there no difference between cohesional and chemical forces as some maintain?

The phenomena. It was long ago observed by Scheele and Fontana independently that a good grade of animal or plant charcoal (charcoal made by heating cocoanut shells is particularly good) had the property after it had been freed of gases by heating in vacuo and then cooled while in the vacuum, of taking up a quantity of any gas to which it was subsequently exposed. This is the original process to which the term adsorption was applied. The gas thus adsorbed or bound to the charcoal could be obtained unchanged by the use of the air pump and by heating the charcoal. The process in other words was reversible. If a given weight of charcoal was taken it was found that the amount of gas adsorbed was variable with the gas and was less at any temperature as the critical temperature of the gas was lower. Thus at any temperature helium was least adsorbed and then followed hydrogen, argon, nitrogen, oxygen, carbon monoxide, methane, carbon dioxide, ethane, chlorine and sulphur dioxide (22) in the order named, sulphur dioxide being condensed at the highest temperature and being the easiest to adsorb. The adsorption, in other words, is specific and varies from gas to gas. Not all the gas is adsorbed at even low pressures.

The process goes only to equilibrium. The adsorption is greater at low than at high temperatures; it is exothermic and it is reversible. Various samples of charcoal vary in adsorptive power, and the greater the surface the greater is the amount of gas taken up. But a sample which adsorbs one gas well, adsorbs also all the others well. Finally the nature of the adsorbent plays a part. Charcoal is perhaps the best adsorbent of gases, but silica gel is also very good. It must not, however, be heated too high or it loses its power.

If a given weight of charcoal is exposed successively to varying quantities of gas, i.e., varying pressures of gas from very low to about an atmosphere, the temperature being kept constant, it will be found that at very small pressures a considerable proportion of the gas has been adsorbed when equilibrium is attained. As the pressure increases a less proportion of the gas, but more absolutely is taken up, and as the pressure rises while more is taken up the proportional amount is less and less. If we plot these results with the pressures as abscissas and the amount adsorbed per gram as ordinate a curve rising at first very fast is obtained, but it gradually bends over. There are no sharp points of inflection, or discontinuities. This curve is known as the "isotherm," that is the equal temperature curve. This isotherm may be expressed for a considerable portion of its course by the formula

$$x/m = kc^{1/n}$$

where x/m is the amount of gas adsorbed per gram of adsorbent, m being the weight in grams of the charcoal; k, is a constant; c, is the pressure of the gas when equilibrium is obtained; and n, is a number lying usually between 2 and 5.

This isotherm is supposed by some to be characteristic of a physical as contrasted with a chemical process, but as Arrhenius (1) has pointed out, it has in reality no such significance. It is simply the equilibrium curve of an easily dissociated compound and it says nothing at all concerning the nature of the forces holding together the different dissociating constitutents of that compound, such as the adsorbent and the gas. These forces may be either chemical or physical. The fact, therefore, that a compound dissociates so as to follow this curve, does not mean, as some have supposed, that the compound is held together by forces of cohesion rather than by chemical forces. It is because this erroneous meaning has been attributed to the isotherm that so many authors speak of adsorptive compounds as necessarily physical rather than chemical. The union between oxygen and hem-

oglobin and between carbon monoxide and hemoglobin for example is a true chemical union showing proper stoichiometric relationships, yet it follows this isotherm exactly. And the process of adsorption of gases by solids is generally physical, yet it also follows this isotherm. The isotherm, therefore, does not permit any conclusion as to the nature of the forces. It shows only that we are dealing with an easily dissociable compound in a mobile equilibrium so that it is reversible and which may be either chemical or physical.

This formula for the isotherm it has now been found (1) does not actually express the real facts except for a limited part of the course. Always the adsorption approaches a maximum value. The substance becomes saturated. In the case of hemoglobin this is when all the hemoglobin has been converted to oxyhemoglobin, and in the case of a solid saturated with a gas it is when the surface of the solid is so completely covered by the gas that the influence of the solid no longer is felt in the outer layers of condensed gas. Arrhenius (1) has shown how the results of Miss Homfray (22), whose work on this subject is particularly worthy of commendation, can be more fully expressed by the formula:

$$\log_{10} \frac{s}{s-x} - 0.4343 \frac{x}{s} = \frac{1}{k} c$$

x, being the amount adsorbed per gram; s. the maximum value of x; c, the pressure; and k a constant.

The nature of the forces involved. In the adsorption of gases by charcoal are the forces holding the gas on the surface surface tension forces, or chemical affinity, or cohesion? Or are we dealing with a solution of the gas in the solid? All of these views have had their advocates. Miss Homfray (22), for example, has shown how her results could be treated mathematically by applying to them van't Hoff's treatment of dilute solutions. She considers the gas as dissolved in a solid solution and the solid as if it acted as a strongly supercooled liquid. However it is certain that while the matter may be treated mathematically with some success in this way, in reality the process itself is nothing of the kind. It is certain that gases penetrate such solids as carbon or the metals or glass with extreme slowness. Otherwise gases could not be contained in glass or metal containers. But the equilibrium of the gas with the condensed gas is obtained in a very few minutes, indeed much of the adsorption takes only a few seconds, so that the process canot be primarily one of solution of the gas in the solid.

The various attractive forces of nature thus far recognized are gravitation, cohesion including adhesion, chemical attraction, electrostatic, electromagnetic and magnetic attraction. If we consider which of these forces is active in the adsorption of gases we conclude as follows: Gravitation may be at once discarded for it is so weak a force that it could not possibly explain the phenomena. Electrostatic and electromagnetic and magnetic attractions may also be discarded. Neither the neutral molecules of the gas nor the solid bears any appreciable electrical charge, nor is there any relation between magnetism and condensing power. The attraction between gas and adsorbent must be, therefore either chemical attraction, as has been suggested by many and recently by Langmuir (26), (27), or it must be cohesional attraction (1), (67). That it is not chemical in the particular cases we are considering is shown by the fact that gases with no chemical affinity such as argon, are condensed just as strikingly as any other gases. Nitrogen, argon, oxygen, carbon monoxide and methane are similar in their adsorbability at $-78°$. These gases are so widely different in their chemical properties as to show that there is no relation or at any rate no primary relation between chemical properties and adsorbability. There is left, therefore, only cohesion or adhesion. The force which is active in this case of adsorption, namely the adsorption of these gases by charcoal, and also of most liquids by solids, must be, by exclusion, the force of cohesion. This fact was first pointed out, so far as I can find, by Titoff (67), and it was particularly investigated and dwelt upon by Arrhenius (1) in a very interesting article entitled "The fundamental laws of adsorption." Titoff pointed out that there was a close relation between the value of the constant a of van der Waals' equation and the adsorbability of gases. Now a of van der Waals' equation is nothing else, as the author showed (34), (38), than the quantity of cohesion, or the mass factor of the cohesion, so that practically Titoff's suggestion was that gases were adsorbed proportional to the amount of cohesion in their molecules. He showed that those gases which were most easily condensed, and so had the most cohesion, were most easily adsorbed. Adsorption became, therefore, practically a process of liquefaction of the gases.

The author's studies of cohesion (34), (37), (38) permit now a much more accurate consideration of the whole process. Consider the state of affairs at the surface of a solid or liquid. In the first place, how does a solid differ from a liquid? What happens at the melting point? We may provisionally adopt the following explanation of the

solid state. Solids are solids for two reasons: *a*, because their molecules have a larger amount of cohesion in them than the molecules of bodies which are liquids at the same temperature; and *b*, because their molecules depart from the spherical form. That is, of two substances with the same quantity of cohesion in their molecules it is probable that that one of which the molecules depart most widely from the spherical form will melt at the higher temperature. The importance of molecular form in determining solidity is shown by the different melting points of stereoisomers. The reason why form is of importance is probably that the melting point is that temperature at which the molecules are driven so far apart by their kinetic motions that they can revolve freely, the molecules of liquids being in rotation (23). The mean distance between the molecular centers must at the melting point become equal to, or slightly greater than the longest diameter of the molecule. I may make the importance of form clearer by considering oleic acid and stearic acid. The former is a liquid at room temperature; the latter a solid. These two substances have the same quantity of cohesion, within very narrow limits. Oleic acid has a little less cohesion, but very little. The form of the molecule is different and there are reasons for thinking that the molecule of stearic acid is relatively stiff and rigid, whereas the double bond in the oleic acid is a point of weakness and permits the molecule to double over (21), (26), acting like a hinge, so that the length of the molecule is not more than half that of stearic acid. Its longest diameter is only half that of the latter and consequently the molecules get sufficiently far apart to revolve at a lower temperature than in the case of stearic acid. But, although the form of the molecule is of importance, the principle difference between solids and liquids at the same temperature is that solids have the more intense cohesion. *It is this very fact of high cohesion in solids which enables them to condense these gases on their surfaces.*

Let us consider now the condition of the surface of a solid or liquid. The situation may be pictured as follows: (unpublished observations). The amount of cohesion in a molecule may be represented by a certain number of lines of cohesional force which radiate in all directions from the center. The molecule may be pictured as cubical. The same number of lines of force leave each face of the cube. These lines of force go only as far as the next layer of molecules (9), (48), (38). They must be neutralized or saturated there, just as the electrical lines of force are saturated by the surface upon which they abut.

Each species of molecule has a definite power of neutralizing the cohesional lines of force, and it can neutralize just as many lines as it sends out and no more. Now at the surface of a solid or liquid, the outwardly directed lines of force of the surface molecules have in a vacuum nothing nearby to saturate them, as there are no molecules lying close beyond them and they must abut on something. Consequently they bend over and abut on the exterior surface of the molecules lying next to them in the surface, as is shown in figure 1. These lines of cohesional force are assumed to repel each other and to con-

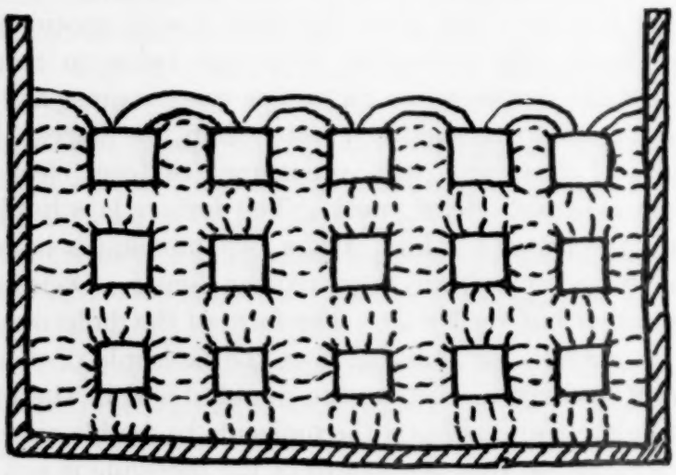

Fig. 1. Diagram showing molecules of a liquid united by lines of cohesional force. The peripheral or surface layer has lines of force causing surface tension drawn in in solid lines. Each molecule has from each face four lines of cohesional force.

tract just as those of electricity, to which indeed they are related, so that they tend to shorten. The result of this is that the peripheral layers of molecules are attracted in the plane of the surface not only by the ordinary cohesion, but by the additional force of the cohesion which ordinarily is directed outward. This additional tension in the plane of the surface is what is known as the surface tension. It puts the surface of a solid under strain, and in liquids will draw the liquid into the form of a spherical drop if the mass of liquid is sufficiently small. Now let us suppose that a molecule of a gas approaches the surface of a solid thus constituted. The approaching gas molecule is also surrounded by its lines of cohesional force which tie it to the other gas molecules. The density of these lines of force is of course not

great. But when the molecule is driven by its kinetic energy close to the solid surface it enters the field of force of these surface molecules, and they in turn enter its field of force. This field varies in its intensity in various solids, as we shall see in a moment, but in the case of carbon or charcoal it is very intense so that unless the gas molecule is approaching with great speed so that its elastic rebound will serve to carry it again out of the field, it will stick on the surface and be trapped there, just as the weaker flies stick to sticky fly paper. Each of these molecules so trapped saturate as large a number of lines of force as they carry themselves. The attraction between gas and solid is proportional to the product of the number of lines of force each carries. But a gas like hydrogen carries very few such lines. Its cohesion is very small. It can saturate only a few of the lines of the carbon and as a result a considerable quantity of molecules of hydrogen will be required to saturate the cohesion of the solid. This means that a great deal of hydrogen can be condensed. It is clear also that as the outward directed lines of force of the peripheral layer of molecules of the solid are gradually released from abutting on the neighboring molecules so that they abut on the overlying gas, the surface strain of the surface layer, in other words its surface tension, will be reduced. So that what is called surface tension in a liquid or solid is reduced by the adhesion of the molecules of the gas or vapor. It is for this reason that the principle of Gibbs can be so easily applied to this process. Actually the surface tension of the solid is reduced by the condensation of the gas as Freundlich and others maintain. This, however, it will be observed, is a result, not the cause, of the condensation. The molecules are held on the surface not because they reduce the surface tension, as is generally stated, but because they are attracted by their cohesional attractions to the surface. They are held there by the force of cohesion, not by that of surface tension. The reduction of the surface tension is an incidental result of their cohering to the surface. (For further development, see page 573.)

As all molecules have the same amount of kinetic energy at the same temperature, the number of molecules which can be held by the surface against the force of their rebound when they strike the surface, will be directly proportional at any given temperature in the first place to the amount of cohesion in the gas or vapor molecule; and in the second place to the amount of cohesion in the molecules of the solid. It may also be dependent upon other factors to some extent, such for example as the size of the molecule, which may determine how close the

molecules may approach, and also very likely on a factor corresponding to the influence of the medium in an electrical attraction, a factor which we may call cohesional permeability. But the main factor in determining how many molecules will be held at any temperature by any given solid will be the amount of cohesion in the molecules of the gas.

The exact manner in which the amount of cohesion determines the amount of adsorption is set forth in table 1. In this there is put down

TABLE 1

*Relation between adsorbability of gases and their cohesion**

SUBSTANCE	QUANTITY OF COHESION $\times 10^{-12}$ (FOR GRAM MOL AND ABSOLUTE UNITS) "a"	ADSORPTION, CUBIC CENTIMETER PER VOLUME SYNTHETIC CHARCOAL (CORRECTED PROBABLY TO ZERO DEGREES AND 760 MM.)		
		20°	−78°	−185°
Helium	0.025			15.0
Hydrogen	0.3	7.3	19.5	284.7
Argon	1.7	12.6	92.6	
Nitrogen	1.7	21.0	107.4	632.2
Oxygen	1.8	25.4	122.4	
Carbon monoxide	1.85	26.8	139.4	697.0
Methane	2.92	41.7	174.3	
Carbon dioxide	4.37	83.8	568.4	
Nitrous oxide	4.9	109.4	330.1	
Acetylene	5.16	135.8	488.5	
Ethylene	5.93	139.2	360.7	
Ethane	6.71	119.1	275.5	
Chlorine	7.66	304.5		
Sulphur dioxide	7.75	337.8		

* Figures for adsorption taken from Bancroft, *Applied Colloid Chemistry*, p. 5. The figures for *a* of Helium and Argon are less accurately known than the others.

under "a" the amount of cohesion in cohesional units (C.G.S. units) possessed by a gram mol of the gas in question as determined by the author (34); and along side the amount of gas adsorbed at the same temperature. An inspection of this table shows that not only do the gases follow the same order, but also there is an approximate proportionality between the two values. Helium, containing extremely little cohesion, is adsorbed least; argon now takes its proper position, being adsorbed as expected from its cohesion; hydrogen, nitrogen, oxygen

and the others follow just in the order they should. Possibly chlorine and sulphur dioxide are adsorbed a little more than expected, but the adsorption is measured below the critical temperature of these two gases, and possibly some reserve chemical affinity may reenforce the cohesion in their case. This will have to be determined later. In fact it can be predicted with a certain degree of accuracy how much gas will be adsorbed.

Indeed this method now opens a way for the direct determination of a of van der Waals' equation from the adsorbability of the gas. This experimental determination should be extremely valuable. But I have not yet derived the theoretical relationship between "a" and the number of molecules adsorbed at any temperature.

The specificity of adsorption for which there has hitherto been no adequate explanation, is then explained. It is the varying amount of cohesion in the gas.

The amount of cohesion in the various molecules in the foregoing table is expressed in cohesional units. Unit quantity of cohesion has been defined by the author as that quantity of cohesion possessed by a hypothetical molecule of the weight of one gram, having therefore a molecular weight of 6.06×10^{23} and possessed of 6.06×10^{23} valences or chemical combining equivalents. The reasons for this definition are given elsewhere. (Unpublished observations.)

The specificity of the adsorption power of the solid is also now explained. It is the amount of cohesion per molecule of the solid which primarily determines its adsorbing power toward these particular gases. If we have two solids of the same porosity and extent of surface, one of them having a very high cohesion, and the other a relatively low cohesion, that solid with the higher cohesion will adsorb best. For example, at the temperature of solid hydrogen there can be no doubt that charcoal will prove a far better adsorbent for helium than will solid hydrogen itself. For the latter has a very low cohesion; the former a very high one. Charcoal adsorbs extremely well at these low temperatures as Dewar pointed out. If cohesion was a chemical process one would expect adsorption at such low temperatures to be diminished or slowed instead of increased. The solids which are the best adsorbents have all of them a very high cohesion. They melt at very high temperatures, showing in this way the intensity of their cohesional fields. They are charcoal, silica and platinum. Solid ether, solid alcohol, fat, substances which have a relatively low cohesion have also very poor powers of adsorption.

We may also in passing and in order to get a clear idea of the difference between cohesional and chemical forces, consider for a moment the nature of cohesion. What is it in a molecule which determines its quantity of cohesion? There are two factors which determine the quantity of cohesion in a molecule (38). One of these factors is the amount of gravitation it has, in other words its gravitational mass. Other things equal the heavier molecules cohere best. This is shown very clearly if we compare fluorine, chlorine, bromine and iodine. The first two are gases or vapors at ordinary temperatures and pressures; the third is a liquid; and the fourth is a solid. The quantity of cohesion increases with the gravitational mass. The other factor is the amount of chemical affinity which the molecule has. This quantity, its chemical mass, is expressed, or seems to be expressed, as this point is not entirely certain, by the ratio of the number of valences (chemical combining equivalents) to the molecular weight. For example, the most reactive element, that one with the greatest amount of chemical affinity is without doubt the negative electron. This has one valence and a molecular weight of 1/1845. It may be said to contain 1845 units of chemical affinity; the next most powerful is the positive electron, the hydrogen nucleus. This has a valence of unity and weight of unity. It has unit quantity of chemical affinity. Argon has approximately one valence and an atomic weight of 40. It has 1/40th of a unit. Oxygen has 1/8th of a unit and so on.

If C is the amount of cohesion in cohesional units, the author found that the quantity of cohesion in any molecule was expressed by the following formula;

$$C^2K = (m^2k \times Val/Wt)^{2/3}$$

In this formula K is a constant of proportion, the cohesional constant, being equal to $k^{2/3}$ or 1.643×10^{-5}; m, is the gravitational mass in grams; k, is the gravitational constant, of the value of 6.660×10^{-8}; Val is the number of valences, the sum of the valences of the atoms composing the molecule; and Wt is the molecular weight.

a of van der Waals' equation is equal to N^2C^2K, where N is the number of molecules of the gas for which a is determined.

It is clear from the foregoing that cohesion is not identical with chemical affinity, as Traube, Langmuir, Harkins, and some others have supposed. Cohesion differs from chemical affinity in two particulars. Cohesion varies inversely with the 4th power of the distance; whereas the force of chemical affinity varies apparently as the square.

Chemical affinity is either electrical or magnetic, and probably the former. Cohesion is neither of these. Chemical affinity appears to vary directly as the number of valences and inversely as the atomic weight, whereas cohesion varies directly as the molecular weight, that is directly as the gravitational mass. Cohesion involves both gravitational affinity and chemical affinity.

Having found a method of computing cohesion let us now compute what the strength of the field at the surface of charcoal will be. Some assumptions are necessary but probably a result of the correct order of magnitude can be obtained. We shall assume that the cohesion is due to the molecules of carbon, which will be taken as C_6, and we shall disregard the other constituents, silicates, phosphates, etc., which are usually present. The diameter of a molecule of C_6 will be taken as 5×10^{-8} cm. From the formula

$$C = (m^2 \times Val/Wt)^{1/3}$$

and assuming that the law of adhesion is the same as that of cohesion, what will be the attraction between hydrogen gas and the surface? m, for C_6 is $72 \times 1.662 \times 10^{-24}$; Val = 6×4 or 24; Wt is 72. For hydrogen, H_2, C_H would be $(2 \times 1.662 \times 10^{-24})^{2/3}$. C for carbon, C_6, would be then 1.68×10^{-15} cohesional units; and for H_2 2.08×10^{-16}. If then a molecule of H_2 comes within a distance of 3×10^{-8} cm. of a molecule of C_6 the two will attract each other cohesively as $CC'K/r^4$ or as C' is the cohesion of H_2 $1.68 \times 10^{-15} \times 2.08 \times 10^{-16} \times 1.643 \times 10^{-5}/(10^{-8} \times 3)^4$ dynes, or 616×10^{-6} dynes. And if the number of molecules in 1 sq. cm. of the surface is 4×10^{14}, each molecule of C_6 having an area of 2.5×10^{-15} sq. cm. the cohesive attraction between a layer of molecules of hydrogen on the surface of a layer of molecules of C_6 so thick that the cohesion of the carbon is saturated would be 2.30×10^{10} dynes per sq. cm. Or as there are 1.0132×10^6 dynes in an atmosphere, this would be a force equal to 22,700 atmospheres. Of course this tremendous pressure would be effective only if the molecular centers could approach within a distance of 1/2 the sum of their diameters or of 3×10^{-8} cm. The force falls off very rapidly so that already at a distance of 10^{-7} cm. the attraction between two such layers of molecules would have fallen to about 184 atmospheres, owing to the 4th power law. This shows that the molecules will cohere only when they are practically in contact with each other. Let us suppose a molecule of hydrogen approaching the surface with the mean velocity of a molecule at zero degrees C. Its kinetic energy at that

temperature will be 3.74×10^{-14} ergs. If it approaches within 3×10^{-8} cm. of the carbon molecule it will be attracted with a cohesive energy of 2.28×10^{-13} ergs. It will be seen from these figures that the slow moving molecules will be captured and held by the cohesive attraction of the carbon so that the surface will come to be covered with a layer of hydrogen molecules which are held under a pressure of several hundred or even several thousand atmospheres. As the temperature falls, more and more molecules will be captured and retained, as their kinetic energy is no longer able to effect their evaporation from the surface. A condensation constantly increasing with the fall of temperature will occur. Finally at some temperature the surface will be entirely covered by a layer of hydrogen molecules probably one layer thick. From this time on the cohesion is diminished to about that of condensed hydrogen. The influence of the adsorbing solid will be no longer felt, and the surface will behave like one of condensed hydrogen. At the critical point of hydrogen, i.e., 33° Absolute, the critical pressure is 12.8 atmospheres. The internal or cohesive pressure is perhaps 6.5 times this or say 83 atmospheres. The attraction, therefore, between liquid and vapor of hydrogen is very small compared to the attraction between solid charcoal and hydrogen.

Conclusion: The foregoing considerations show that the adsorptions of gases and vapors by such solids as charcoal in the instances specified, is due to the intense cohesional fields of the solids. The union between the adsorbent and the adsorbed is brought about by the force of cohesion. There is a close parallelism between the quantity of cohesion in a gas molecule and the number of such molecules which can be retained by any solid on its surface. This variation in cohesion of different gases explains the specificity of the adsorption, in these cases. The cohesive field of the solid is also of importance and all good adsorbents, such as charcoal, silica gel and talc, have very high cohesions. The cohesive field at the surface of charcoal is at a semi-diameter of a molecule from the surface of the order of magnitude of 20,000 atmospheres.

In addition to adsorption of gases by cohesion, chemical forces also may in some instances come into play, through reserve valences, to increase the force of attraction. Two clear cases are known to the writer, namely, the adsorption of oxygen and carbon monoxide by hemoglobin. These are adsorbed chemically to the colloidal hemoglobin. The cohesive fields of neither of these gases is sufficiently intense to explain their adsorption. Their cohesion is between that

of nitrogen and methane and neither of these latter gases is appreciably adsorbed by hemoglobin at the temperature of the body. In the cases of O_2 and CO and hemoglobin, therefore, an additional attractive force of a chemical nature, which is much more intense than cohesion, comes into play. The molecules of O_2 and CO are chemically united with the hemoglobin as is shown by the change in the spectrum, by the change in crystalline form, and by the exact stoichiometrical relationships which exist when the hemoglobin is saturated. One molecule of oxygen or one molecule of CO is taken up at the maximum and no more; and the compound is obtained in a crystalline form.

While most cases of adsorption of gases by solids are therefore cohesional and hence physical, others, and particularly these two of such great physiological interest, are chemical. The fact that the isotherm has the same characteristics in the two cases shows that Arrhenius is correct in concluding that the form of the isotherm indicates nothing as to the nature of the forces holding the dissociable compound together. The isotherm means only that those forces are not intense, but that the compound is readily dissociable, the amount undissociated being determined by the pressures of the constituents.

THE ADSORPTION OF SUBSTANCES IN SOLUTION AT THE SURFACES OF LIQUIDS IN CONTACT WITH GASES. This is the phenomenon which is usually considered to be the type of all adsorptions and to be of particular importance in protoplasm. Since it is necessary to get a clear concept of the nature of surface tension in order to understand the problems which arise, we may begin by considering the relation of surface tension to cohesion.

1. The relation of surface tension to cohesion. By reference to the diagram on page 566, figure 1, it is seen that surface tension is produced by the fact that the surface molecules are unequally attracted outward and inward. The surface molecules of a liquid in contact with its saturated vapor do not have their peripherally directed lines of cohesional force entirely saturated by the molecules of the vapor, owing to the low density of the latter, but these lines bend laterally and abut on the neighboring molecules of the surface, thus setting up an additional tension or strain in the plane of the surface which constitutes the surface tension. This gives the surface the property of an elastic, stretched solid exerting the tension of an elastic skin on a drop of the liquid as soon as it becomes spherical. The amount of this surface tension, or extra pull in the plane of the surface, will be determined by the number of lines of force which are directed into the

plane of the surface instead of outward, and this will be determined by the difference in the number of molecules in the liquid and the gas or vapor, in other words by the difference of density of the liquid and vapor. As the cohesional pressure per square centimeter varies as the square of the density, the differential of pressure constituting the tension will be proportional to the square of the difference of density of liquid and vapor (37). When the density of the vapor equals the density of the liquid, as it does at the critical temperature, there will be no surface tension.

It is generally stated in text books of physics, if they notice the subject at all, that the relation between cohesion and surface tension is unknown, but in reality a limited solution of the problem was made by Thomas Young one of the earliest writers on the subject of capillarity and cohesion over a century ago but his conclusions in this direction appear to have been overlooked by most writers. Young stated that the surface tension energy of unit surface was equal to one third of the total cohesive pressure of a stratum of particles as deep as the distance to which the cohesional attraction penetrates. Putting this in the form of an equation we have

$$S = Kr/3$$

S being the surface tension energy per unit of surface; K being the cohesive pressure per square centimeter, represented by van der Waals later as a/V^2; and r, is the radius of action of the cohesional force. Now since Young in deducing the formula neglected the cohesion of the vapor and considered only that of the liquid, this formula holds only at that temperature where there is no vapor, in other words at absolute zero. The true relation which holds for all temperatures was found by the author (37). It is obtained by multiplying the right hand member of the equation by $(T_c-T)/T_c$. It is as follows:

$$S = (ad_o/3MN^{1/3}V^{2/3})(T_c-T)/T_c$$

or by slight rearrangement,

$$SV^{2/3} = (ad_o/3MN^{1/3}T_c)(T_c-T)$$

V is the volume of a gram mol of the liquid at the temperature T; a, is van der Waals' constant, that is the quantity of cohesion in a gram mol of the liquid; d_o, is the density at absolute zero; M, the molecular weight; N, the number of molecules in a gram mol; T_c, the critical temperature; T, the temperature at which the surface tension, S, is

measured. This formula is nothing else than the empirical formula found by Eötvos, correlating the surface tension and the temperature:

$$SV^{2/3} = C(T_c - T)$$

C is a constant having the value, usually, in non-associating substances of about 2.15. The significance of C is shown by inspecting the previous formula, to be $ad_o/3MN^{1/3}T_c$. And $Kr/3$ is $ad_o/3MN^{1/3}V^{2/3}$. This formula practically says that the surface tension energy is a function of the difference in cohesive energies of the vapor and liquid.

2. The depth of the surface film. How deep is the film in which surface tension exists? We have to know this before we can get any idea as to how much substance it can dissolve. van der Waals showed that in such a layer there is a diminution of density as one passes toward the vapor. This layer has been measured in various ways, and computed in other ways, and it is found to be a function of the temperature, being deeper as the temperature rises. At ordinary temperatures for water, it is about two, or at the most three, molecular layers deep. It increases slowly in depth until quite near the critical temperature when it increases very rapidly, becoming as deep as the vapor at that temperature. The number of molecular layers is probably given by the formula (37)

$$(d_o/(d_1 - d_v))^2$$

It is clear from this that the amount of liquid in the surface film is extremely small. The total depth is hardly greater than the diameter of the smallest colloidal particle, being of the order of magnitude of 10^{-7} cm. That is about one ten millionth of a centimeter. At the most it is not more than 10^{-6} cm. There can, therefore, be extremely little substance dissolved in the surface film.

3. Adsorption in the surface film. The surface tension is the intensity factor of the free energy of the surface. Willard Gibbs pointed out, in virtue of the general principle already discussed on page 557 that any substance dissolved in a liquid so that the surface tension of the solution was lower than that of the pure solvent would concentrate in the surface film, for by so doing it would reduce the intensity factor (the surface tension) of the surface energy. But it will be observed that while by so concentrating it lowers the intensity factor of the surface energy, it increases the intensity factor of the osmotic energy. Consequently if it remains in solution, it can only accumulate until the increase in the intensity factor of the osmotic energy, the osmotic

pressure in other words, just equals the decrease in the intensity factor of the surface energy. In virtue of this fact, and also because of the extremely minute amount of liquid in the surface film, extremely little accumulation of substances is to be looked for in the surface film, particularly when the very small surface tension changes which are possible are considered. And it may be said at once that only very minute changes in concentration can be produced in this way, as long as the substance remains in solution.

But if the solubility of the substance is not high, so that the limit of solubility is passed before the equilibrium of lowered surface tension and increased osmotic pressure is attained, there will be a continuous separation of the solid substance at the surface. If the substance thus separating is colloidal it will form a membrane on the surface, this membrane being composed either of the solid colloid itself, or having a gel structure; if, on the other hand, the substance is crystalline, such for example as calcium carbonate, or various dyes or other substance of low solubility, it may separate in crystals, and in particular in small spherocrystals. The formation of a scum on milk, when it is heated; the formation of membranes at the surface of protoplasm; the formation of a solid soap layer in a soap film or in a soap bubble are instances of accumulations of this kind. And no doubt the deposition of calcium salts of various kinds at the surfaces of animals may be due to a similar process of secretion (70). Protective membranes tending to separate the phases may thus be produced. By this very simple method an individual is rendered to some degree independent of its environment and a great step forward in securing freedom from that environment, in other words the first step forward in evolution of primitive protoplasm, was taken.

In this way then shells, bones, spicules of minerals, nuclear membranes, ectoplasm and other membranes may be produced by the continued secretion into the surface layer of substances which lower the tension of that layer and which by their insolubility are prevented from reaching equilibrium (32), (70).

Another very important result of this accumulation of colloidal substances which thus forms a coherent membrane, or even a gel, at the surface, is that it greatly increases the viscosity of the surface film. It has been found by various observers that if a magnetic needle is suspended in the surface film it will move into the magnetic meridian very much more slowly, in the case of soap and many other solutions, than if it is suspended beneath the surface. This viscosity of the surface

is only marked in the case of those solutions containing colloids which have the property of lowering the surface tension of the boundary of solution and vapor or air. The viscosity of the surface layer of a solution of sodium chloride is not greater than that of the solution itself.

This increase in the viscosity of the surface layer, due to this process of secretion, if we may so call it, is of very great interest. It is the reason, probably, that the ectoplasm of nearly all cells is tougher, more membranous, more like a gel, than the endoplasm; and that the nuclear membrane is tough. It is this surface viscosity also, which causes liquids to foam. Foaming is the physical characteristic of a soap solution. All solutions which foam do so because their surfaces have a high viscosity; and the higher the viscosity the more stable is the foam. The viscosity of the surface film of a soap solution is so great that it is almost a solid. The foaming of blood when air is drawn through it, is due to the same cause; and indeed it is probable that the power of making emulsions of all kinds, such for example as that of protoplasm itself, is due to this secretion of substances of a colloidal nature into the surface film with a resulting great viscosity. The film may actually come to be solid and its viscosity prevents it from rupturing. For foaming, then, two things are necessary, namely the presence of colloidal material which lowers surface tension so that it accumulates in the film, and second the high viscosity of the film produced by the presence of this material. If it be desired to prevent foaming in a liquid all that is necessary is to add to the solution some substance which will reduce the surface viscosity. It is possible that the pharmacological action of certain alcohols, anesthetics, and other "capillary active" substances with low surface tension may be due in part or wholly to this action as Traube has suggested. Lee also found that minute amounts of alcohol reduced fatigue in muscle and he thought this might be due to a reduction in viscosity of the protoplasm. There are, however, so many other possibilities of the action of these substances and the parallelism between their surface tension lowering powers and their pharmacological action is so incomplete that it is impossible as yet to make a definite statement on the subject.

On the other hand it is clear that the accumulation of a substance like alcohol, or ether in the surface of separation of water and air, must be very minute, for these substances do not precipitate there, and they quickly reach an equilibrium between surface tension lowering and osmotic pressure raising.

Another matter of very great interest is the orientation of molecules in the surface film. It has been shown by Harkins (21) and also by Langmuir that the molecules of a fatty acid, when they lie on the surface of water, orient themselves so that the carboxyl group is in the water, and if the acid is saturated and has a long chain of carbon atoms, as for example palmitic acid, the rest of the molecule arranges itself perpendicularly to the surface. The molecules thus take a parallel or palisade arrangement in the surface. The carboxyl group is called a "polar" group, but we might also call it hydrotropic. Is it not interesting that the carboxyl end of the molecule of a fatty acid seeks the water, just as the growing roots of a willow seek water? How similar such a molecule, with its jointed, segmented body is to an annelid, or a shrimp! It even has a gradient of irritability in it like an earthworm, being most reactive at the carboxyl end, as the author has pointed out. In oleic acid the molecule bends down in the middle where the double bond is to bury this in the water also. This orientation of molecules at the surfaces of such films, if it occurs at the surface of protoplasm, as it may, but has not yet been shown to do so, might be of great importance in the passage of substances through the surface film; it might be of great importance in the passage of the nerve impulse and the electrical wave; and in the secretion or absorption of water by the cell. It is possible that it may be at the bottom of the striated appearance of the limiting membranes of the intestinal cells.

Another phase of this matter which may be touched on here is the nature of the gels which are formed at the surface of soap solutions. It was shown by Clowes (8) that in an emulsion of oil, a little soap and water, that two forms of emulsions exist, namely, water in oil; and oil in water. In the first case the oil is the outer phase and completely surrounds the water; in the latter case the water is the external phase and surrounds the oil. Clowes has found that emulsions of this character, particularly at their transition points where they are about to pass from one kind to the other, are affected by salts just as is protoplasm. And on such emulsions he shows the same antagonistic action of salts which has been studied for cells by Pauli, Loeb, Osterhout, Lillie, Mathews, Koch and others. Clowes suggests that in protoplasm there is such an emulsion with the oil the external phase, but very near its point of transformation. However were this the case water soluble substances could not penetrate protoplasm, so it is certain that the picture, while it explains many phenomena, is not yet complete. Fischer (10) has suggested that the difference between a

soap sol and a soap gel, is that in the sol the water is the external phase of the emulsion; whereas in the gel the soap is the external phase. It is possible that in the external membrane of the cell a transition may occur from the one kind of emulsion to the other, but this while suggestive has not been proved. However the remarkably interesting observations of Kite (25), and in particular of Chambers (7) on the micro-dissection and micro-physiology of cells, point clearly in this direction. The great difficulty comes in transferring to such a mixed emulsion as protoplasm, which is in contact with water and penetrated by water, the results and conceptions coming from a study of the phenomena of the simple surface of separation of a solution and air.

4. Explanation of the process. The exact mechanics of this surface condensation or adsorption is not yet clear. The fact that the energy relations are satisfied gives us no picture at all of the mechanism of the process, and before we really understand it we must have such a picture. It is possible that it is due to the drawing inward, in consequence of their greater cohesion, of the solvent molecules, leaving the solute behind in the surface. All the substances which thus accumulate at the boundary of water and air have a lower surface tension than water.

5. Conclusion. The surface film of a liquid in contact with its vapor is at ordinary temperatures only two or three molecular diameters deep. It can therefore dissolve only a very minute amount of substance. The accumulation of any substance in this film, that is its adsorption, will be extremely small as long as the substance remains in solution; for the accumulation can only go to the point where the change in surface tension is balanced by the increase, or decrease, in osmotic pressure. But if the substance is little soluble, or if it forms a gel, a continuous secretion can take place at the surface and probably the surface membrane of protoplasm, is produced in this way, at least in part. However this has not yet been proved. Also some change in distribution of substances in cells may be produced in this manner as Macallum has suggested. It cannot be said, however, that any such instance has as yet been proved.

The mechanics of the process of accumulation is not explained by the principle of energetics cited to explain it. The reduction of surface tension by the passage of these substances into the surface, is a result of their accumulating there; it is not the cause. The cause probably is that the cohesion of the solvent molecules is greater than the adhesion of the solvent for solute, or the cohesion of the solute, and as a consequence the solvent molecules are drawn in from the surface, leaving the solute concentrated in the surface.

SURFACE TENSION AND ADSORPTION AT THE BOUNDARIES OF SOLID AND LIQUID. The conditions at the surface of a solid and liquid do not differ in essentials from the condition at the surface of vapor and liquid phases. But the surface tension cannot be measured at the boundary of solid and liquid. It is entirely erroneous, therefore, to proceed, as most have done, and to carry over to such cases results which have been obtained from the study of a surface of a liquid in contact with its vapor. How can it be predicted whether a substance in solution will accumulate at the surface of separation of solid and liquid, if nothing is known of the tension at that surface and still less of how the tension will be effected by the entry into the surface of a third substance? While the tension of the liquid in contact with a solid cannot be measured we may deduce certain conclusions in regard to it. And in the first place it is certain that the surface tension of most liquids in contact with most solids is *negative*. This follows from several considerations: *a*, positive surface tension, such as occurs at the boundary of liquid and air, is due to the greater attraction inward, as compared to the outward attraction, of the surface molecules; *b*, adhesion appears to follow the same laws as cohesion; *c*, because the cohesional fields of most solids are greater than those of most liquids. Consequently the peripheral layer of molecules of a liquid in contact with a solid must be attracted outward to the solid more than they are inward. The differential of pressure is then directed outward, rather than inward as it is at the surface of liquid and air and as a result of this the surface tension of the liquid will be negative. The liquid will spread over the solid and increase its surface to a maximum. Furthermore the liquid in contact with the solid will become more dense, often, than the rest of the liquid, and this will force any gas, soap, or capillary active substance out of this layer. In fact it is in virtue of this cohesional field of a solid being intense that the solid is able to condense vapors and gases on its surface. And for he same reason when a solid is taken out of a liquid which wets it, and a liquid will wet any solid in which the attraction of the molecules of the liquid for the solid is more than half that of the liquid particles for each other (see Young), a layer of the liquid remains attached to the solid. It is only a few liquids of high cohesion, such as mercury, which will not spread on some solids and in particular such as are covered by a layer of air. In all other cases the surface tension of the liquid in contact with the solid is negative. We do not know how negative it is, although an approximation may be made by computation. So far as I know such computations have not been carried out.

The surface tension of the liquid being negative, we cannot say that because a substance accumulates in the surface film of the liquid in contact with air, where the tension is positive, that it will also accumulate in the surface film of a liquid in contact with a solid. As a matter of fact it will usually be negatively adsorbed here. Michaelis and Rona (45) have recently shown that the adsorption of capillary active substances, such as some alcohols, is so small with most adsorbents that it cannot be detected whereas it is usually stated in books on adsorption that it is at a maximum for such substances.

The surface tension of the solid in contact with a liquid is reduced from what it is in contact with air. The surface tension of the liquid is usually negative, when it abuts on a solid; but the surface tension of the solid usually remains positive. The algebraic sum of both these tensions is positive except for substances which dissolve. When the sum of both solid and liquid tensions becomes negative, then not only will the liquid spread on the solid but the solid will spread on the liquid and solution will take place. This is probably what determines solubility; at least it is one of the factors as Gibbs pointed out.

Suppose now alcohol, or ether, or any other substance of a lower surface tension than water is in water in contact with a solid, let us say glass. Will the alcohol and ether or gas move into the surface of contact or will they move away from it? It is ordinarily stated that they will move into it (See Macallum, (32) p. 618). As a matter of fact they must move away from it and their adsorption will be negative. At this surface the differential of pressure in the liquid is now outward, whereas it was inward in the gas-liquid boundary. The adhesion between glass and alcohol is less than between glass and water. Water will displace the alcohol or ether from the boundary and move to the solid. It is a very similar case to that of the earth. As it stands in contact with the ether, air, liquids and light solids of small gravitation move to the surface. But if another planet came in contact with the earth, these same light substances would move out of the zone of contact.

And on the other hand salts, such as sodium chloride which have a greater cohesion than water, will move into the surface of contact of liquid and solid and be slightly concentrated there. Their adhesion to the solid is greater than water, and they will tend to displace the water. The relations will be just the contrary to those usually asserted. Furthermore the substance thus adhering to the surface of the solid in virtue of the force of cohesion alone, will really be adhering to the solid.

It will not be simply dissolved in an adherent layer of liquid as has been stated.

The adsorption by most solids of capillary active substances is so slight that as a matter of fact Michaelis and Rona (42) could discover none at all for most adsorbents. It was only in the case of charcoal and talcum that a very slight adsorption of octyl and decyl alcohol could be established. Furthermore a basis is thus given for the adsorption of KCl at the interfaces in cells as shown by Macallum (32). This observer together with Miss Menten precipitates potassium by sodium cobaltonitrite, and subsequently converts the precipitated cobalt salt into the sulphide which has a dark color and can be seen in cells. Where this precipitate occurs it is assumed that potassium was. Chlorine shows much the same distribution so that the salt is supposed to be potassium chloride. Macallum interprets the peculiar distribution of the cobalt sulphide precipitate as indicating how potassium chloride is distributed by surface tension through the cell. If this precipitate is really due to potassium and not to ammonium or other base, the foregoing considerations show that the potassium might be distributed by adsorption in the manner Macallum has contended. However there are so many unknown factors and so many possibilities, that any certain conclusion is impossible.

Conclusion. We may now put the question which has been in our minds from the beginning. Suppose that we find that a substance in solution concentrates at the surface of a solid which is in contact with that solution. It is positively adsorbed in other words. Can we conclude from this fact that it accumulates there because it lowers surface tension? Or can we conclude that all substances which accumulate at such surfaces will be those which accumulate at the surface of contact of the solution with air? Or can we conclude anything as to the state of surface tension at the point where accumulation occurs? To all these questions there is but one answer to be given: *No.* In no case can we draw a positive conclusion. For as we have seen, substances may stick to the surfaces of solids either because they are held there by forces of chemical attraction, or by forces of adhesion. We can say nothing as to the nature of the forces because the substances are found there. But of one thing we can be certain: *In no case do they accumulate there because they lower the surface tension.* Such a lowering may be a result; it is certainly not the cause. Sodium chloride will move somewhat into the boundary of charcoal and water. This is not because it lowers the surface tension; but it is because it

is held by cohesion more firmly to the solid than is water and so it displaces the water. But this accumulation will not be very great; it will be very small, for by moving into the surface its concentration there will be increased and osmotic pressure will prevent its accumulation. Above all, nothing can be concluded, as Macallum concludes, that because any substance, such as potassium chloride, accumulates at one part of a cell, that it does so because the surface tension is lower there than some where else. Let us suppose we have a cell made of glass at the sides and the two ends made of graphite or charcoal. Suppose we have potassium chloride in solution in water in such a cell. Where will the potassium chloride accumulate most? In the first place since it is soluble the accumulation will be extremely minute anywhere. The cohesion of the graphite is presumably greater than that of the glass. Consequently the sum of the surface tensions of the water and the solid will be greater in the case of the water-graphite boundary, than for the glass-water boundary. Or in other words glass will have a greater tendency to dissolve in water than will graphite. Now how will the potassium chloride behave? It will concentrate somewhat in the surface film, for its cohesion is greater than that of water. We will leave out of account the chemical substitution which may take place at the surfaces of either the glass or the graphite. *The chloride will concentrate most on the graphite,* so far as its concentration is due to its cohesion, for the graphite has the greater cohesion and will attract it most strongly. In other words it accumulates where the surface tension is highest, not where it is lowest, as Macallum (32, p. 618) suggests it should do. In this respect therefore his reasoning is wrong. By its accumulation it will indirectly reduce the thermodynamic potential, but the cause of its accumulation is not the lowering of the surface tension; it is its adhesion. And the only other force which we have to consider is its chemical or electrical or magnetic attraction for the surface. Much that has been written on positive adsorption by solids of substances from solution, must be entirely rewritten, as it is erroneous. A substance positively adsorbed at a water-air surface, will be negatively adsorbed at most solid-water surfaces.

As a matter of fact most cases of this kind of adsorption are due to still more powerful affinities, namely those of the atoms themselves. They are adsorptions due to chemical affinity; to chemical substitutions. And these we may now consider.

CHEMICAL ADSORPTION OF SUBSTANCES FROM SOLUTION BY SOLIDS. Under this heading are found most of those cases of adsorption with which we are familiar, such as decolorization by the use of charcoal; staining and dyeing; tanning; the precipitation of proteins; precipitation of one colloid by another; capillary analysis by means of filter paper. All of these are cases of adsorption, for the reason that the adsorbing substance is of a coarseness at least equal to that of the smallest colloidal particle in diameter. Consequently all of these substances make with the solvent an heterogeneous or diphasic system. But this however does not alter their chemical powers, and in most or all of these adsorptions there can be little doubt that chemical substitutions rather than forces of surface tension, or physical forces, are involved. I shall take up only a few of these for criticism.

Let us take up to begin with the decolorization of solutions of dyes by charcoal or filter paper. It is well known that basic dyes are more easily adsorbed by filter paper, or rather usually more basic dye is taken up, than of an acid dye. This is generally treated as if it were a typical case of adsorption, for the reason that the dye can be obtained again from the paper by washing out or extraction with alcohol. It was found by Freundlich and Loser (12) that when methylene blue was adsorbed by charcoal, an amount of chlorine corresponding to the methylene blue adsorbed (47), methylene blue being a chloride, was found in the wash water. This process has now been studied further by Michaelis and Rona (41) with very interesting results. They find that the purer the filter paper, the less is the adsorption. The adsorption is determined by, and the amount goes proportional to, the amount of calcium or other silicate in the paper. It is the ash which causes the adsorption not the filter paper. The same thing is true of charcoal. This discovery destroys at once the whole surface tension theory. It shows that adhesion, or cohesion, has nothing to do with the matter, since cohesion is not materially changed by extracting the mineral substances. Furthermore it turns out that in the filtrate when charcoal is the adsorbent one always finds an amount of potassium or other mineral ion replacing the basic colored ion adsorbed. These facts show in the clearest manner that this adsorption is, as has been always maintained by the author, a true chemical adsorption, the base of the dye chemically substituting the base of the adsorbent. Furthermore the presence of the divalent calcium permits the adsorption of some acid dye as well as a base, one valence of the calcium getting free to attach the acid dye.

The staining of wool in dyeing or the staining of sections of animal tissue is also, as the author long ago showed (35), a process of chemical adsorption. Wool is a protein. It contains free amino groups and also a few free carboxyl groups. The former are basic and will bind acid; the latter will take up bases reacting with them to form salts. Now the dyes, acid or basic, do not differ from other salts in their fundamental properties. If we add acetic acid to wool, the acetic acid unites with the protein in the manner described presently, in the amino groups, and by ionization of the salt thus formed the protein becomes positively charged. This protein will then unite chemically with an acid dye, since the colored part of the molecule in such a dye is negative, to form a salt which is colored. And similarly in an alkaline solution the wool will be electro negative. It will then unite only with basic dyes, since in them the colored part is electro positive. The physical adsorptionists (4) try to save this case as a physical adsorption, by saying that it is a physical force, namely the electric charge, which causes the adsorption and that this is a case of adsorption due to electrical charges. So it is, but so is also the adsorption of chlorine by a sodium ion. Yet no one denies that the force holding the sodium and chlorine together in sodium chloride is chemical. And so it is here. Haller (16) has particularly shown these to be chemical unions but because solvents may separate the constituents he interprets them as not being chemical.

Another simple case of adsorption is probably the adsorption of acid by filter paper. If one place on filter paper a drop of dilute acid, the peripheral part of the drop will be found not to be acid in reaction. The acid remains in the center surrounded by a halo of water. What holds the acid there? The colloid chemist says that it is a case of adsorption. So it is, but this explains nothing. In this case the forces holding the acid are probably chemical. The colloid chemists give two explanations of the matter. On the one hand they say it is due to surface tension concentration of the acid at the phase boundaries. It concentrates there because it lowers surface tension. And on the other hand it is explained that the acid is adsorbed because the hydrogen ion is very easy to adsorb. But why the hydrogen ion is easily adsorbed is not explained. We may put the surface tension theory to the test by preparing two dilute solutions, one of sodium chloride, the other of hydrochloric acid of the same surface tension. Now make a wick of filter paper and let the water flow by capillarity from the wick. It will be found that the first drops from the acid are water

and not acid; on the other hand the first drops from the sodium chloride always contain the salt. It seems impossible to separate salt from water by filter paper, but acid can be separated. The surface tensions were the same. Evidently the physical explanation is erroneous or at least incomplete. Prof. J. U. Lloyd told the writer that he had carried the wick clear up two stories high and down in an attempt to separate water from salt by this method, but always the first drops contained salt. The explanation probably is that given by Stieglitz and incorporated in the author's textbook (36). It is that ether oxygen, such as exists in polysaccharides, is quadrivalent. It unites with acids, because such oxygen is slightly basic. The acid is held in this way. It is well known that the hydroxyl alcohol and the amino groups are closely similar in their properties. And since the latter are known to bind acids, so may the former. Also some acid compounds of methyl ether have been isolated in a crystalline form. Oxonium salts are well known. Furthermore it is also known that acids hydrolyze polysaccharides becoming free again after hydrolysis (49). The most probable explanation of this process is that they unite with the substances upon which they act, just as they unite with the proteins which they similarly hydrolyze. In other words the chemical explanation of this adsorption is in consonance with all known facts and it is much clearer, as showing just where the union takes place, than the physical. And the physical has no evidence in its favor.

Another very similar case of chemical adsorption is the adsorption of acids by proteins with the resulting change in the sign of the charge. This phenomenon is explained by most colloid chemists who have written of it, with the statement that hydrogen ions are very easily adsorbed and that being adsorbed they give the protein the positive charge of the hydrogen. This statement is correct only in so far as acids are readily adsorbed by proteins. The rest of the statement is incorrect. Furthermore the adsorption is due to a chemical union as has been shown by Kossel, and many others. The amount adsorbed is proportional to the free NH_2 groups. The adsorption does not occur because of any ease of adsorption of the hydrogen ion. This ion is no more easy to adsorb than any other. It all depends on the adsorbent. It is very easily adsorbed by basic adsorbents, but not by acid. The free amino groups of the albumin are basic in character. They have the property by increasing the valence of the nitrogen of adding acids, just as NH_3 adds acid. The sole difference is that in the case of protein the molecule is so large that it makes a heterogeneous

solution, whereas ammonia is a small molecule. Being united with the amino group, the chlorine is dissociated leaving a positive charge on the nitrogen atom from which it separates. The positive charge is thus obtained. This gives a clear cut, chemical, readily understood explanation in consonance with all the facts. To say that the protein gets its charge by adsorbing the hydrogen ion, which for some unknown reason is particularly easily adsorbed, explains nothing, gives no clear picture and no clew to an experimental verification.

Furthermore the reversal of the sign by putting the protein in alkali is not due to the fact that the protein adsorbs the hydroxyl ion, which is usually said to be particularly easy to adsorb, owing to some unknown and imaginary effect on surface tension. The change in sign is due to the fact that proteins are acids also. When alkali is added a chemical reaction occurs, the metal salt of the protein being formed. The metal ionizes leaving a negative charge on the carboxyl oxygen of the protein. This simple explanation covering all the facts has been so befogged by many colloid chemists that even they themselves could not find their way in the fog of their own making.

A typical case of chemical adsorption is the adsorption of alkaloids by Lloyd's reagent, an aluminum silicate. This reagent is finding great use in the preparation of alkaloidal tablets. If one adds this reagent to a solution of an alkaloid, the alkaloid is adsorbed and precipitated. It sticks entirely in the reagent. In this case the chemical nature of the process is shown by a variety of facts. In the first place the reagent will adsorb only basic substances, or it adsorbs by preference basic, that is positively charged, substances. It will adsorb basic dyes far better than acid. In fact it will hardly take up the latter at all. This shows that it is not a matter of adhesion or of surface tension, for there is no class difference in the adhesions and surface tensions of acid and basic dyes. Furthermore that the adsorbed substance is in the form of the salt is shown by allowing Lloyd's reagent to adsorb a substance which is colored as the salt but not as the free base. Some plant colors are basic and have this peculiarity. In such cases the adsorbed dye has its color of the salt form, not that of the free base. And in addition it will be found that if the wash water is examined the acid part of the alkaloidal salt, such as sulphuric or other acid is in the filtrate. A decomposition has occurred. This adsorption is then due to chemical forces.

Among the many interesting cases discussed recently by Pauli (54) showing how so many colloids get their charges by processes

of ionization, in a manner identical with the explanations given by the author (36), the case of starch may be mentioned. It has long been known that starch contains phosphoric acid (60), but usually no mention is made of this fact. It is this phosphoric acid which most easily gives the negative charge to colloidal starch by ionization. If the amylose is separated from the amylopecten which contains the acid, the pure starch has very little negative charge. It is neutral or very nearly so. In fact most of the substances studied by colloid chemists have been such mixtures, such as charcoal, filter paper, etc., that it is hard to interpret results.

Finally reference should be made in closing to the rectification of another erroneous view which has been recently made by Pauli (54). It has been believed that the different colors of the gold sol which might be blue or red were simply a matter of fineness of subdivision of particles. The view has been that gold sol consisted of gold particles negatively charged by their sending positive gold ions in solution. It was observed that the different colored sols had different colored particles and these were of different sizes. The erroneous, or rather the unfounded, inference was drawn that the difference in color was due to the difference in size of particles. In most metals it is known that a difference in color betokens a change in valence of the metal as for example, copper or iron. This has now been shown to be the case also by Pauli, the gold being held in colloidal solution by some of the aurate and having the negative sign of this anion. The color change is due to the change in valence of the gold from mono to trivalence.

Conclusion. I am well aware that this treatment of this part of the subject is incomplete and quite contrary to the views generally held. But the prevailing views, so far as the fog which exists in the field permits any view at all, are distorted. It is clear that the force causing the adhesion of substances to the surfaces of solids must be usually either the physical force of adhesion, or the chemical one of chemical affinity. If it is the latter then the compound which is formed is a definite chemical compound, whether it can be isolated or not. And it leads only to confusion to treat of it as if it were a compound of some other nature. As a matter of fact most authors deal with these compounds as if they were not chemical compounds but physical. This gets them at once into difficulties, for the extreme specificity of the reactions, the clear cut substitutions of one base or acid for another, pointing clearly to a chemical union, remain wholly unexplained. They are forced to fall back on their favorite

explanation, namely, that the case is one of specific adsorption and let it go at that. In fact the whole subject at the present time is a perfect morass and those who wander in this field with physical adsorption for their lantern climb out of one mud hole only to fall into another. In no field does this happen more frequently than that of dyeing and the staining of fibers, or the precipitation of proteins. There seems to be some innate objection on the part of Freundlich, Ostwald and other colloid chemists to considering proteins as if they were chemical compounds. When a thing is a colloid it at once is treated as if it had lost all its chemical properties. As a result it is impossible to understand why wool colors itself in an alkaline bath with basic stains and in an acid bath with acid dyes. Fanciful explanations must be adopted based on the wholly supposititious greater ease of adsorption of one ion than another, an ease of adsorption for which no explanation whatever is given. All the phenomena are predictable, and readily understood, on the basis of a chemical union, and they are not explicable on any other theory known to the writer.

I may cite one other example of the increasing confusion which the use of the word adsorption in the sense of a physical rather than a chemical union produces. This is in the field of pharmacology. Several recent papers have appeared dealing with pharmacological facts as if they involved physical adsorptions. There have been two papers recently by van Leeuwen (74), (75) which are typical of the the work in this field. The facts are very simple. Something in rabbit's serum, or in the serum of some rabbits, neutralizes the action of atropine and pilocarpine. It has been known for many, many years, that rabbits were unusually immune to atropine. Now it is found that it is possible by extracting the serum with alcohol to recover again nearly all the atropine in the alcohol. This valuable observation is interpreted to mean that it is a case of adsorption. Colloids, those magic things, have magicked the atropine, have translated it so that it was for a time quite different from what it usually is. The authors explain the fact by calling it a case of adsorption. That is all there is to it. Colloids certainly seem to have magic powers, but I believe the magic is exerted not on the drug which is investigated, but on the investigator. Like Bottom he is translated. In the case in point nothing whatever is gained by calling it an adsorption. This gives only the appearance of an explanation. The serum is full of colloids, most of them protein; but unfortunately so is the serum of all other animals, which have no such powers of neutralizing the atropine.

Consequently there must be something curious about the colloids of rabbit's serum, if indeed it is an adsorption. These then must have a specific peculiarity, namely that of a specific adsorption for atropine. This should content anyone. It seems to content colloid chemists. It leaves us exactly as wise as we were before. And a similar satisfaction in labeling some process an adsorption is found in the vast majority of the papers dealing with the processes of adsorption. One comes back, as does the author, from an excursion into this field filled with pessimism. If this is indeed science, he at least, wants none of it.

PHYSIOLOGICAL APPLICATIONS OF ADSORPTION. In closing, space only permits the pointing out of a very puzzling physiological phenomenon which may be explained in a satisfactory manner by adsorption. I refer to the secretion of hydrochloric acid in the stomach. How from a living cell hydrochloric acid as strong as 0.1 N could be secreted has always been a puzzle. The idea that it is secreted by the parietal cells of the fundus glands, at any rate in the form of acid, although chlorides may be formed here, was disproved by the observations of Bensley and Harvey. It is impossible to get any strong acid by any of the chemical decompositions such as those of carbonic acid, lactic acid, or phosphoric acid, which have been suggested. It is impossible that the juice could be formed in the cell itself, for in order that it should be 0.1 N after dilution by all the other secretions of the stomach, it would be necessary to have the parietal cells secreting at least normal HCl, that which would be an absurdity. Or at any rate a greater miracle than what we are attempting to explain. It was suggested by the writer that in reality the secretion was similar to the formation of acid in solutions of ammonium chloride by various moulds (36). They absorb the ammonia and leave free hydrochloric acid in the medium. If the limiting cells of the stomach acted similarly this would explain the formation of acid. The difficulty was to understand the process of absorption of the ammonia. This may be understood as follows, as first suggested I believe, by Bechold (4). If manganese dioxide hydrate is added to a solution of potassium sulphate, the sulphate becomes decomposed. The potassium is adsorbed by the manganese oxide and the hydrogen ion of the colloid becomes free in the medium so that free sulphuric acid is formed. It is necessary if this is to happen that the ionization of the potassium compound should be small. Lloyd's reagent acts similarly, and Lloyd states that when an alkaloid is precipitated from a solution of its salt free acid remains in the solution. Silicic acid will act in this way. If, therefore, the

outer border of the lining cells of the stomach were colloids of similar properties to these inorganic colloids, they might decompose in this way sodium chloride or ammonium chloride leaving hydrochloric acid outside the cell. The main difficulty in this explanation is how the sodium salt is regenerated into the acid colloid which is required. Perhaps carbon dioxide has something to do with this. At any rate this makes possible a partial understanding of a very difficult problem.

Bancroft suggests that the adsorbent is not in reality acid, but that the salt is hydrolyzed into base and acid, and that then the free base, in this case it would be sodium hydrate or ammonium hydrate, is adsorbed by the colloid. Why it is adsorbed is not explained. It is another of that infinite number of specific adsorptions.

SUMMARY

1. The word adsorption means only that there occurs at the boundary of the phases of a heterogeneous system a change of concentration of some substance from its concentration in either phase. If the concentration is increased in the boundary it is positive adsorption; if diminished, it is negative. The word implies nothing as to the nature of the forces or of the process which brings this change of concentration to pass. The assumption that it means a physical rather than a chemical force is incorrect.

2. Modern work shows that this change of concentration is produced in some cases by cohesion, in others by surface tension changes, and in perhaps the vast majority of cases of adsorption of substances from solution, it is due to chemical forces.

3. The attempt to bring all these processes under one head, namely that of surface tension, has failed and has led to confusion.

4. Gases are adsorbed on solids owing to the intense cohesive fields of the solids. They are held by the force of cohesion and there is a close parallelism between the quantity of cohesion in a gas or vapor and the amount adsorbed. These unions are then physical. The specificity of these adsorptions is due to the varying amounts of cohesion in the gases. Solids which adsorb best are those of the greatest cohesion. This explains a large part of the specificity of the adsorption power of solids.

5. The adsorption of carbon monoxide and oxygen by hemoglobin is not due to cohesion or surface tension, but to chemical forces.

6. The forces of chemical affinity and of cohesion differ in various particulars and are not the same. Cohesion varies inversely as the

4th power of the distance; chemical attraction probably inversely as the square. Cohesion involves both gravitational mass and chemical affinity, the amount of cohesion in a molecule being proportional to both of these attractions. Chemical affinity probably varies inversely as the atomic weight and is proportional to the quotient of the number of valences divided by the atomic weight. The forces of cohesion and chemical attraction are not therefore identical as often supposed.

7. The quantity of cohesion in a molecule is given by the formula

$$C = (m^2 \times \mathrm{Val}/\mathrm{Wt})^{1/3}$$

in which C is the quantity of cohesion in cohesional units, unit quantity of cohesion being that amount possessed by a hypothetical molecule weighing one gram and having 6.06×10^{23} chemical combining equivalents or valences. m, is the gravitational mass in grams; Val is the number of valences; and Wt is the molecular weight.

8. The relation of cohesion to surface tension is given by the formula

$$S = (ad_o/3\mathrm{MN}^{1/3}\ V^{2/3})\ (T_c - T)\ /T_c$$

This embodies the formula of Thomas Young and expresses also the well known law of Eötvos, with the value of the constant written out. a, is van der Waals' constant, which has the value of N^2C^2K, C being the amount of cohesion, K a constant and N the number of molecules in the mass of gas for which a is determined.

9. The fact that alcohol or ether or other so called capillary active substance concentrates in the film between liquid and air does not permit the conclusion that it will concentrate in the film between solid and liquid or between liquid and liquid. On the contrary such substances will avoid the film between solid and liquid, and substances like sodium chloride will collect there, but only to a very slight degree.

10. The surface tension of a liquid in contact with a solid is nearly always negative. It is for this reason that the liquid spreads over the solid. The surface tension of the solid in contact with a liquid is much lower than in contact with air, but remains positive. When the sum of the negative surface tension of the liquid and the positive surface tension of the solid becomes negative the solid dissolves in the liquid.

11. To what extent the distribution of substances in protoplasm is controlled by the action of the substance on the surface tension at the boundary of different phases in the protoplasm cannot be stated. The most that can be said is that such an influence is possible.

12. It is probable that the surface membranes of all cells are produced in part at least by this process of secretion from a solution upon its surface of substances which lower the surface tension of the interface and are sufficiently insoluble. It cannot yet be said however that there is any proof that this is the case since the relations between protoplasm and the surrounding liquid in which it is placed are so complex that an analysis cannot yet be made. However the quick coating over of the surfaces of the amoeba's pseudopodia, looks as if such a process occurred.

13. The adsorption of non electrolytes from solution by solids is probably due to cohesion.

14. The adsorption of most other substances from solution including acids, bases, ions, salts, dyes, etc. is due to chemical forces, the adsorbed substance forming a true chemical union with the surface molecules of the solid. It is for this reason that only basic dyes are adsorbed by acid adsorbents and only acid dyes by basic adsorbents. The process of dyeing is a process of adsorption, but it is also a process of chemical adsorption, and can be best understood on the latter basis. The specificity of the adsorption depending on the chemical nature of both adsorbent and adsorbed substance is thus explained. The fact that exact equivalent proportions of constituents are not found on analysis, does not show that the forces are physical and not chemical. It shows only that the substance analysed is a mixture.

15. It is not possible to conclude from the isotherm of adsorption that the process is chemical or physical. The isotherm shows only that one is dealing with an easily dissociated compound in a moving equilibrium. Both chemical and physical dissociable compounds follow the same isotherm.

16. The colloids get their charges not by adsorbing ions as is customarily said, but by chemical additions and subsequent ionization of the compound. The current explanation that proteins become positive in acid solutions because they adsorb hydrogen ions, these being easy to adsorb, is ambiguous, and essentially untrue.

17. An explanation of the formation of hydrochloric acid in the stomach is given on the basis of adsorption.

18. It would seem wholly superfluous to point out, were it not that the contrary assertion is constantly encountered in papers on adsorption, that when a solution of a compound is shaken with a non-miscible solvent in which one component of the compound is soluble, but the other is insoluble, and it is observed that one of the constituents of the

compound can be separated in the solvent, so that the compound is broken up, this fact throws no light at all on the nature of the forces holding together the constituents of the compound in the original solution. It is wholly incorrect to infer from this that the compound is not chemical, for many chemical compounds are known which can be decomposed in this way. It is wholly incorrect to infer that one is dealing with an adsorption compound, for the constituents may neither one of them be colloidal. All that this experience shows is that the compound is dissociable, that it exists in equilibrium with the products of its dissociation, and if one of these elements is constantly removed by the nonmiscible solvent, eventually the whole of the compound will be reduced to its constituent parts.

19. The word adsorption is useful in one respect. It enables us to speak of agglomerations or compounds or mixtures without committing ourselves to any conclusion whether these are physical mixtures or chemical compounds. But we must always remember that when we have called a thing an adsorption complex, we have confessed our ignorance of any understanding of the process, rather than attained any idea as to its nature. The next necessary step must be always, as it has been in the past, the isolation of the compound concerned in its chemically pure form. It is only when this has been done, that a real step forward has been taken. The attempt to explain the action of drugs or physiological mechanisms by calling them 'adsorptions' is a step backward, except in so far as this word signifies that the drug or protoplasmic substance has entered into a dissociable union in equilibrium with its constituents.

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THE VITAMINS

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The literature of the vitamins has grown to such proportions that in order to write a physiological review within the available space it seems best to confine the discussion chiefly to such of the work upon vitamins as is of present importance to normal physiology. This will mean that little attention can here be given to the historical development of the subject, to its strictly pathological aspects, or to the somewhat extended though as yet inconclusive investigations which have been directed to the study of the chemical isolation of the vitamins. Some references to these phases are included in the appended bibliography.

To Hopkins we owe the first clear statement (102) backed by convincing experimental evidence (103) that normal nutrition requires food sustances other than those comprised among the proteins, fats, carbohydrates, and the compounds of the mineral elements. Through the work of Osborne and Mendel, McCollum and Davis, Holst and Fröhlich, Hess and others it was established that there are at least three of the essential "accessory substances" whose existence Hopkins had demonstrated. Meantime the term vitamine, introduced by Funk (68) in connection with his study of experimental beriberi was becoming current as a general designation for these previously unknown food constituents. Because of certain objections to this term, McCollum proposed the names "fat-soluble A" and "water-soluble B" as temporary designations for two of these substances to which "water-soluble C" was soon added. In order to simplify the situation Drummond has proposed (36) a terminology in which the word vitamin (the final e being omitted to avoid the implication that the substance is necessarily a nitrogenous base) is retained as a group designation and the letters as a means of distinguishing the recognized members of the group until such time as chemical names may be justified. Following this suggestion, the three substances will be known as vitamins A, B, and C in this review. In the following pages each of these three vitamins will be considered in turn.

VITAMIN A

As early as 1881, Voit pointed out (211) the desirability of feeding experiments with mixtures of known substances rather than with the unknown mixtures which constitute our ordinary natural articles of food. Simultaneously Lunin (117) reported feeding experiments with mice designed to study the nutritive significance of the inorganic constituents of food. Failing to obtain with any of his known mixtures results comparable with those shown by animals fed upon milk, he concluded that the latter must contain some unknown substance of importance in nutrition; but this suggestion, offered somewhat incidentally and without convincing evidence, can hardly be regarded as constituting a discovery of the existence of such unknown food substances or of their indispensability in normal nutrition.

This discovery was announced in 1906 (102) by Hopkins, who, however did not publish his evidence until 1912 (103).

Hopkins found that young rats on diets of purified proteins, fats, carbohydrates and salts soon showed nutritive failure, whereas the addition of milk, fresh or dry, or of the alcohol-soluble substances of milk to such a food mixture rendered it adequate for normal nutrition and growth. Stepp in 1909 also showed (200) that some unknown alcohol-soluble material is essential to nutrition. Osborne and Mendel in 1911 (152) confirmed Hopkins' finding and extended it by feeding experiments with "protein-free milk" and in 1913 McCollum and Davis (127) and Osborne and Mendel (153) independently found that with rations otherwise satisfactory young rats would grow or fail to grow according as the fat in the food mixture were butter fat or lard—evidence of the presence of a fat-soluble, growth-promoting substance in milk and butter fat which in lard is either absent or present only in much smaller amounts. In another paper published later in the same year, Osborne and Mendel (154) pointed out that animals suffering for lack of this fat-soluble substance (vitamin A) become subject to an eye disease which has since been widely discussed in connection with this dietary deficiency under the names of ophthalmia, xerophthalmia, keratomalacia, and conjunctivitis.

Effects of a lack of vitamin A. In the case of each of the three vitamins now recognized, the characterization of the substance, and in fact the belief in its actual existence, depends chiefly upon the physiological disturbances observed to follow the use of a diet deficient with respect to the vitamin in question. When a diet lacking vitamin A but adequate

in all other respects is given to a young growing rat, growth continues for a shorter or longer time, probably because of stores of this vitamin which the body already possessed, after which growth ceases and, if the diet is entirely devoid of the vitamin, there usually sets in a loss of body weight and a condition of general decline leading to death. Sometimes, perhaps because the experimental diet contains unrecognized small amounts of vitamin A, the body weight remains nearly constant and the animal apparently in health for some time after growth has ceased. By the time the body's reserves of vitamin A have been exhausted and growth ceases the animal shows increased susceptibility to bacterial infection, and this lowered resistance results in a large proportion of the experimental animals developing the characteristic disease of the eye. This usually begins with a swelling of the lids of one or both eyes or with indications that the eye is becoming unduly sensitive to light. Following this there commonly develops an inflamed and catarrhal condition of the conjunctivae, with a bloody or purulent discharge, the lids becoming scabby or sticky. This, with the swelling of the lids and the sensitiveness to light, sometimes results in the eye being found completely closed. If the eye condition is not treated and the animal continues to live, the cornea may become affected and blindness result. The typical condition undoubtedly involves infection and, according to Bulley (8), may be prevented by careful treatment with antiseptics, though Osborne and Mendel found that their cases were not cured by such treatment (172). Since eye trouble resulting from lack of the A vitamin involves infection, it is not purely a deficiency disease, yet it is essentially such inasmuch as the dietary deficiency enormously increases the susceptibility of the animal to the infection, and thus practically determines whether or not the disease will occur. It is also very significant that without any local treatment whatever the eye disease, if not too far advanced, usually disappears quickly upon feeding the animal with any food containing an adequate amount of vitamin A. Thus Osborne and Mendel stated as early as 1913 (153, 154) that "Another type of nutritive deficiency exemplified in a form of infectious eye disease prevalent in animals inappropriately fed is speedily alleviated by the introduction of butter fat into the experimental rations," and in 1914 (155) they reported "uniform success by substituting cod liver oil for a portion of the lard in our standard diets. . . . . Not only was growth resumed in most cases at a very rapid rate, but all evidence of malnutrition, especially the affection of the eyes, promptly disappeared." Similar cures were also observed by Osborne

and Mendel in the following and subsequent years and have since been reported by many other investigators whose work is reviewed by Osborne and Mendel in their recent paper on ophthalmia and diet (172). As the animals approach maturity their requirement for vitamin A becomes relatively less as indicated by the fact that they can remain in health for a longer time upon a diet deficient in this respect. In how far this means a real diminution in the vitamin A requirement and in how far it implies that the older and larger animal, if he has previously been well fed, has a larger store upon which to draw in such emergencies is not yet clear. The solution of the question is complicated by the fact that our usual criteria become less serviceable as the young animal approaches maturity since growth has now nearly ceased and it is reasonable to suppose that the conjunctival tissue will be less sensitive in an animal which has made a normal growth and development than in the young, growing individual. Full-grown rats when placed upon diets lacking the A vitamin are less likely to develop the characteristic eye trouble, but if the experiment is sufficiently prolonged eye trouble appears in a considerable proportion of cases (35), (62), (131), (154), (172), (198), (199), (212).

The relation of the eye disease to this dietary deficiency has been experimentally demonstrated in other species as well as rats (78), (151) and special interest attaches to the question as to whether the use of dietaries poor in the A vitamin may be a factor in the susceptibility to eye trouble in man. McCollum (125) writes: "There are several instances of the occurrence of conditions described in the literature as xerophthalmia, which seem to be beyond question cases in which the disease has occurred in man as the result of specific starvation for the dietary essential, fat-soluble A." The reports here referred to are those of Mori (147) in Japan, whose cases of xerophthalmia occurring among children at a time of food shortage could be cured by feeding chicken livers (liver being rich in vitamin A) and those of Bloch (6), whose cases among the children of the Danish poor also responded to the feeding of foods rich in the A vitamin. Wells (215) found in Roumania, and Dalyell (107) in Vienna, cases of children suffering from eye trouble which was cured by cod-liver oil and presumably arose from a deficiency of vitamin A in their food. And recently McCollum, Simmonds and Parsons (137) have attributed "night blindness," an eye trouble of frequent occurrence in northern regions, to the use of diets poor in this vitamin. The xerophthalmia observed by Bloch (6) among Danish children was regarded as one phase of their

condition of malnutrition. The eye disease appears to have been quite definitely related to deficiency of vitamin A in the diet since it was cured by feeding with whole milk or with cod-liver oil, and in 1918 the disease nearly disappeared from the community coincidently with the general introduction, by government action, of butter into the dietary of the poorer people. Seasonal variation of the incidence of the disease was studied and it was found to be most prevalent in the season of most rapid growth. As xeropthalmia is caused by the absence of something essential to growth, it is clear that the disease will predominate during that part of the year when the organism consumes the largest quantity of vitamin for its growth. Bloch also suggested that vitamin A may be necessary for the formation of antibodies against infection and may be continually used up in this process as in growth.

That lack of vitamin A may lead to weakness or abnormality of other tissues as well as those of the eye has been shown by the work of several investigators. Osborne and Mendel (172) refer to diarrhea and diminished appetite as frequently resulting from this lack; and they have definitely correlated it with the occurrence of phosphatic renal calculi among their experimental animals (160). McCollum and Davis (127), (128) and also Drummond (35) report increased susceptibility to infections including lung disease. Steenbock, Sell and Buell (197) confirm this and suggest that the failure to develop the characteristic eye disease in some cases may be due to a certain immunity acquired through the pulmonary infection. These authors also refer to abnormal cutaneous conditions involving the tail, ears, nose, and sometimes the feet and fur.

With so much laboratory evidence of widespread weakening of the body tissues through lack of the A vitamin, it is not surprising that different writers find reason to correlate a deficiency of dietary supply of this essential with an increased susceptibility to such diverse diseases as rickets, pellagra, and tuberculosis. Space does not suffice for a discussion of these problems in the present review, but references are included in the appended bibliography (35), (37), (70), (91), (92), (97), (106), (126), (136), (138), (144), (145), (178), (179), (185), (187), (188), (198).

Distribution of vitamin A in the body and in foods. McCollum and Davis in 1913 originally reported this substance present in butter fat and the fat of the egg yolk but not in lard or olive oil (127). Osborne and Mendel obtained similar results in the same year (153), (154) and in 1914 reported cod liver oil as rich in this property while

almond oil did not show it (155). Later they showed it to be present in considerable amounts in beef fat, especially in its softer fractions "oleo oil;" also that green leaves such as spinach and alfalfa leaves contain this "fat soluble" vitamin in abundance although they contain hardly any fat. It has been shown both by Osborne and Mendel and by McCollum and his associates that ordinary muscles contain but very little of this vitamin, heart muscle somewhat more, while liver and kidney are much richer in it. In the plant organism the thin green leaf is the part richest in vitamin A; next growing stems or shoots and the embryo of the seed; whilst the seed endosperm and the other storage organs of the plant such as thick roots and tubers are relatively poor in vitamin A. McCollum classifies milk and leaf vegetables as "protective foods" because of their richness in this vitamin and in calcium. It is important to note that milk contains much more of this vitamin than corresponds to its butter fat content. According to McCollum, in a given volume of ordinary whole milk the "fat-soluble" vitamin present is about equally divided between the fat globules and the aqueous portion. Hence skimmed milk is about half as rich in this vitamin as is whole milk. Sherman, MacLeod and Kramer (184) have recently confirmed this finding of McCollum, which unfortunately had been lost sight of by some investigators in the planning of diets which were intended to be practically devoid of this vitamin.

Recent work of Daniels and Loughlin (26) and of Drummond and Coward (39), (42) appears to show that lard and probably other commercial forms of fat supposed to be devoid of vitamin A are not entirely so and that in the case of lard the vitamin content may vary according to the nature of the food consumed by the animal while fattening.

Partly because of the doubt as to whether all of the materials which have entered into basal rations supposed to be free from vitamin A were in fact entirely devoid of this essential, and partly because the capacity of the animal body to store this vitamin must mean that experimental animals will contain variable and sometimes considerable amounts of it in storage when placed upon experimental diet, the interpretation of experiments designed to determine the relative amounts of vitamin A in different foods has heretofore been very difficult and it is doubtful if many of the estimates yet available can be regarded as entirely satisfactory. General impressions of the relative richness of different foods in each of the three vitamins may be obtained from the tables published by the British Committee (106).

Physical and chemical properties. According to McCollum (139) this vitamin, while fat-soluble as obtained from animal sources, is not removed with the fat of vegetable tissues. To explain this he suggested that it might occur in plants in the form of some compound not readily soluble in fat and might become fat-soluble when digested by the animal and thereafter remain fat-soluble in the animal body and in the material separated therein for the nourishment of the young—milk and eggs. Experiments upon the extraction of this vitamin from different materials by various solvents do not seem to have yielded very concordant results. In general vitamin A appears to show such solubilities as would place it in the group of "lipoid" substances. Drummond (35) states that it is not identical with any of the known lipoids or fat constituents. Steenbock and his coworkers have shown that natural food materials rich in yellow pigment usually also show relatively high value as sources of vitamin A (190), (191), (195), (196), (197). While the correlation is not constant (39), (175), (176), (198), yet it seems rather more than accidental and suggests the possibility of some relationship between vitamin A and the natural yellow pigments, particularly carotin. From its apparent resistance to saponification, Steenbock, Sell and Buell (198) hold that it is not a fat and probably not an ester. They therefore conclude as had Osborne and Mendel previously (170) that it should be possible as a means of further investigation to prepare fat-free rations for studies of this vitamin. Vitamin A appears to be readily destroyed when subjected to oxidation, as by vigorous aeration at high temperature or by treatment with ozone (40), (105), (227). As regards its stability toward simple heating the evidence appears somewhat conflicting (35), (157), (184), (192), (194), probably because neither the conditions of heating the material to be tested nor of testing the effects of such heating by subsequent feeding experiments have been well standardized. It is certain that under ordinary conditions this vitamin is not very rapidly destroyed at temperatures near 100°C. Such destruction as will ordinarily occur in from one to six hours at this temperature will probably be apparent in a feeding experiment so arranged as to bring the initial supply of vitamin A very close to the minimum requirement, but not otherwise. In general, foods which contain this vitamin in abundance at the beginning will still be good sources of it after having been subjected to such heat treatments as are involved in cooking, canning, or drying (see McCollum, *The Newer Knowledge of Nutrition*, 1918, pp. 136-137).

VITAMIN B

Effect of a lack of the B vitamin. On diets otherwise adequate but lacking the B vitamin young animals (rats) cease to grow, usually more promptly than on diets lacking vitamin A, and if continued on the diet lacking vitamin B they lose weight and develop a condition of general weakness with more or less distinct polyneuritis. It is generally believed that the growth-promoting substance whose presence in milk was demonstrated by Hopkins and by Osborne and Mendel and to which McCollum gave the name "water-soluble B" is identical with the antineuritic substance to which Funk gave the name "vitamine" in 1912. Eijkmann in 1897 (57) had reported that the lack of such a substance in the diet is the cause of beriberi in man and polyneuritis in fowls, and in 1906 (58) he had discussed it further under the title "nutritional polyneuritis," but it was not until the work of Hopkins, Osborne and Mendel, Funk and McCollum had furnished the basis for a broader conception of the rôle of such substances in nutrition that the true significance of Eijkmann's results could be appreciated.

On the assumption that water-soluble B and antineuritic vitamin are the same, the symptoms of beriberi and experimental beriberi might be described as consequences of a lack of this vitamin. For a full account of such symptoms see Vedder's *Beriberi* (208) and Funk's *Die Vitamine* (70). More recently this subject has been carefully reinvestigated by McCarrison (120), (121). He finds little difference between pigeons deprived of the B vitamin only and those deprived of all three vitamins. As the result of vitamin starvation a slowing of metabolic changes generally and a fall in body termperature were noted. The processes of digestion also were greatly impaired and the intestine was injured. The adrenals were enlarged but other organs lost weight —the thymus most, and then, in order, testes, spleen, ovary, pancreas, heart, liver, kidneys, stomach, thyroid and brain. McCarrison also reports an increased susceptibility to miscellaneous infections as a result of diets deficient in vitamin B. His observations of marked atrophy of testes and ovaries is in line with Drummond's observation (32) that sterility followed quickly in a male rat deprived of the B vitamin; and with the reported tendency to amenorrhea among beriberi women (7). In general the changes found by McCarrison to result from a lack of the B vitamin were fairly similar for birds and mammals. Among the symptoms which he observed in

his monkeys were: progressive anemia, loss of appetite, diarrhea, headache, subnormal temperature, enfeebled heart action, and (usually late in the sequence of symptoms) distinct neuritis. McCarrison believes that his findings "may afford some explanation of the genesis of that great mass of ill-defined gastro-intestinal disorders and vague ill health which forms so high a proportion of human ailments at the present day."

Osborne and Mendel, and more recently Karr in Mendel's laboratory, have repeatedly demonstrated the marked influence of the B vitamin upon the appetite (113).

Detection and measurement of vitamin B. Before attempting to discuss the distribution of this vitamin in the body and in foods, it seems necessary to consider briefly the methods and criteria for determining its presence and relative amounts.

Foods are tested for antineuritic vitamin by determining whether they have the power to prevent or cure polyneuritis in pigeons or fowls and if so the relative amounts necessary to exhibit the same antineuritic effect (106).

For the water-soluble, growth-promoting vitamin the usual test consists in making the food under examination the sole source of this vitamin in a diet otherwise adequate and finding the amount or proportion necessary to induce normal growth in a young rat (165), (166).

A third method consists in noting the effect of the material supposed to contain the B vitamin upon the growth of yeast as measured in one of several ways (2), (54), (55), (64), (67), (71), (111), (118), (119), (150), (189), (205).

As yet it can hardly be said to have been fully demonstrated that all three of these methods or in fact any two of them necessarily measure the same thing.

McCollum has consistently advocated the view that the antineuritic vitamin and the growth-promoting "water soluble B" are the same substance. This view has been generally accepted and is tacitly assumed in the adoption of the term vitamin B to cover both. It has, however, been seriously questioned by Mitchell (146) and by Emmett and his coworkers (63), (64). Obviously it is only on the assumption that these substances are identical that we can accept both the experiments upon polyneuritis in pigeons and upon growth in rats as being measures of the B vitamin.

Similarly the method of testing for this vitamin by measuring in some way the accelerated growth of yeast is enthusiastically adopted

by some investigators as serving the same purpose as the rat growth experiments and in a quicker, more economical and more readily controllable way, while other workers question whether the growth-promoting substance is necessarily the same in the two cases, and if so whether the culture media used for the yeast are so perfect in all other respects as to make it a safe assumption that increased yeast growth may be attributed solely to the vitamin.

Occurrence of vitamin B in the body and in foods. Since the values attributed to different organs and foods as sources of vitamin B have been determined in many cases by different methods, which as above seen may or may not yield properly comparable results, only such statements will be made here as seem to be reasonably established, whatever view be taken of the above questions regarding methods of testing.

The animal body appears to carry no large store of this vitamin. The glandular organs, and eggs and milk, are relatively richer in it than are the muscles. Heart muscle contains more than the skeletal muscles (ordinary muscle meats), which are distinctly poor in vitamin B (136), (159).

In plants on the other hand, as Osborne and Mendel have shown, vitamin B appears in relative abundance in all the chief organs—leaves, stems, roots, tubers, seeds and fruits—(164), (165), (166), (169).

In a series of rat growth experiments by Osborne and Mendel (164), (165), (166), dried yeast appeared richest of the materials tested, dried spinach was about one-fourth as rich as the yeast, and whole wheat, dried eggs or dried milk was about half as rich as the dried spinach. Hopkins (103), (105) finds milk a relatively richer source of vitamin B than do Osborne and Mendel (167).

Physical and chemical properties. Vitamin B is readily soluble in water and in alcohol moderately diluted with water. It is less readily soluble in alcohol stronger than 70 per cent but can be extracted by stronger alcohol when used hot. It is more stable in acid than in alkaline solutions. Only a few quantitative experiments upon its rate of destruction at different temperatures and under different conditions appear to have been attempted. In one of these Chick and Hume (16) found that wheat germ heated two hours at 100° lost little of its B vitamin, while about one-half appeared to be lost in 40 minutes at 113° and up to nine-tenths in two hours at 118° to 124°. These results would suggest that little heat destruction would occur in ordinary cooking but that in commercial canning and sterilizing the losses might

be more serious. In any case a considerable part of the vitamin of the food may be lost by extraction if the cooking water is rejected.

Partly from its solubilities and its greater stability in acid than in alkaline solutions, and partly from the results of attempts at isolation published by Chamberlain, Vedder and Williams (12), Funk (68), (69), Schaumann (181), Suzuki, Shamimura and Odake (204), and Edie et al (56), it appeared probable at a relatively early stage in the study of this substance that it was a nitrogenous base very probably related to the purins or pyrimidins. For a time it appeared probable, chiefly through the work of Williams and Seidell (221), (222), (223) that this vitamin might prove to be a tautomeric form of some known substance, but studies in this direction led to conflicting results (80), (210), (222), (223). More recently Osborne and Wakeman (173) have reported upon a vitamin fraction which they have prepared in quantity from yeast. The further study of this material is awaited with much interest.

Normal physiological functions. The suggested relationship of vitamin to purin or pyrimidin compounds (characteristic of nucleins and "extractives") and the fact that yeast extract, similar to meat extract in general composition, flavor, and property of stimulating the appetite, is rich in B vitamin, as well as the direct observations of the relation of vitamin to appetite above noted, have favored the view that vitamin B may function as a physiological stimulant. Several attempts have been made to connect the vitamin requirement with the metabolism of carbohydrate. Findlay (65) found that in polyneuritic pigeons there is a reduction in the glyoxalase content of the liver by more than one-half that of control birds, followed by an increase in glyoxalase on admininstration of vitamin B, thus indicating a breakdown in carbohydrate metabolism in beriberi. Dutcher (47) holds that "overloading the oxidative mechanism with any energy-producing food will usually hasten the onset of symptoms" of vitamin deficiency, and believes that the vitamin functions "indirectly as a metabolic stimulant." He finds the catalase content of the tissues of polyneuritic birds only about half that of normal birds, from which he concludes that oxidative processes are depressed when the organism is not receiving the normal amount of vitamin (44), (47). He (47) holds it to be not improbable that the depression of body oxidations is accompanied by the formation of toxic metabolic products which affect the nervous system, bringing about the typical paralysis and other symptoms. McCarrison (120), (121) on the other hand calls the

vitamin a *nucleopast* to emphasize the view that it plays an essential rôle in the normal nuclear metabolism. Uhlmann (207) concluded that the vitamin stimulates secretion in the glands of the digestive tract and probably also stimulates the endocrines; that it tends to increased muscular tonus and a dilatation of the vascular tissues with resulting lowered blood pressure. Pharmacologically he considered the action of vitamin to be similar to that of pilocarpine, and the action of atropine to be directly antagonistic to that of vitamin. Dutcher (46), (47) has fed polyneuritic pigeons thyroxin, thyroid, pilocarpine hydrochloride and tethelin. All these substances he found to produce relief and cessation of polyneuritic symptoms but not so promptly as when vitamin was fed. He inclines to the view that the activity of the organs of internal secretion is dependent upon the stimulating action of the vitamin, but holds that it is still a matter of speculation whether this is in the nature of a nerve stimulant, nuclear nutrient, or the chemical nucleus of a hormone.

In connection with the evidence obtained by direct observation upon testes and ovaries of an influence exerted by the vitamin upon the reproductive organs, it is of interest to note that a number of somewhat scattered observations in feeding experiments tend to indicate that normal mammalian reproduction with successful suckling of the young probably requires higher proportions of both A and B vitamins in the food than are required for even rapid growth. Since abundant food intake favors early maturity, fecundity, and lactation (213), (214), it seems possible that a liberal intake of the B vitamin may result in more successful reproduction and lactation partly through stimulating the appetite and thus inducing a larger consumption of all the constituents of the diet, and partly through stimulating or directly nourishing the glands and organs directly concerned in the reproductive processes.

Observations upon lactating animals and upon beriberi women have led to the view that the body does not synthesize the B vitamin and that the mother's ability to supply it to her offspring is dependent upon the vitamin value of her food. The same is believed to be true of the A vitamin also, except that the ability of the body to store relatively large amounts of this latter implies the presence in the body of a well-nourished female of stores of vitamin A sufficient to enable her to supply this to her suckling offspring for a relatively long time in quantities larger than she receives in her food. Since the ordinary rations of dairy cattle are rich in both A and B vitamins at all seasons

of the year, whereas human dietaries consisting largely of highly refined foods are more likely to be deficient in one or both of these respects, it is probable that under modern conditions cows' milk is a reliable source of both of these vitamins, while in order that breast feeding may actually show the superior results that are normally expected from it, it is necessary that the food of the mother shall be properly chosen. Cow's milk with its high proportion of vitamin A, its abundant and exceptionally constituted mineral content, and its highly efficient proteins, should always be a prominent part of the diet of the lactating woman, as has been emphasized by McCollum.

That the body can store vitamin A abundantly, but vitamin B to only a small extent, puts these two dietary essentials in somewhat different categories so far as the economy of nutrition is concerned. Vitamin B must be supplied fairly constantly in sufficient amounts for current needs. In view of its wide distribution among staple articles of food, this calls for no special planning of the food supply beyond the avoidance of too great a dependence upon foods which have been impoverished with respect to vitamin B by milling or other refining processes or by excessive losses through faulty preparation or the rejection of the fluid in which the food has been cooked or canned.

Vitamin A, while much more unevenly distributed among foods and therefore subject to greater fluctuations in the daily intake, is, by virtue of its storage in the body, an asset which can be economically utilized even when received in quantities in excess of daily needs. The dietary should be consciously and consistently planned to give emphasis to foods which are rich in vitamin A, particularly milk and leaf vegetables, which are of special value for this and other reasons as well. And the investment in these foods need not be too closely scrutinized, for any surplus of vitamin A can be stored in the body for future needs and probably also with improvement in stamina and in ability to resist disease.

VITAMIN C

Effects of a lack of vitamin C. Theobald Smith in 1895 noted that guinea pigs kept upon a diet of oats developed a hemorrhagic disease, but this observation did not attract the attention of students of nutrition at the time. Later when Eijkmann and others were showing that a condition corresponding to beriberi could be induced in fowls by faulty diet, Holst and Fröhlich (100), (101) undertook similar experiments in the hope of finding the cause of ship beriberi, which was seriously prevalent among Norwegian sailors.

Believing that their work would be more directly applicable to human experience if they employed mammals rather than birds, they gave special attention to feeding experiments with guinea pigs. It was found that guinea pigs react differently from pigeons or fowls when subjected to a polished rice diet, developing scurvy instead of beriberi. A diet of any other grain or of bread also resulted in a scorbutic condition. Among the symptoms characterizing this experimental scurvy of the guinea pig are: loss of weight, soreness of joints, hemorrhages around rib junctions and knee joints, soreness and hyperemia of the gums leading to looseness of teeth, fragility of the jaw, and other bone changes. The symptoms are clearly described by Cohen and Mendel (21) and will be referred to further in connection with the discussion of the quantitative determination of antiscorbutic vitamin. In view of the recent publication of Hess' excellent monograph on scurvy (90), it is unnecessary to deal further here with the results which follow a lack of the antiscorbutic or C vitamin.

Significance of vitamin C in normal nutrition. Most of our knowledge of scurvy has been gained from observations upon the guinea pig, monkey and man, though the disease certainly occurs in swine, and in all probability in other species also. Is it to be concluded that a species which, like the rat, does not develop scurvy when kept on a "scorbutic" diet is therefore independent of vitamin C and that this vitamin has no function in the economy of such an animal? Evidently such a conclusion would not be justified until after other possibilities have been considered. Harden and Zilva (84) and almost simultaneously Drummond (34) tried the addition of antiscorbutic vitamin, in the form of orange juice, to the diet of laboratory rats and found that such additions result in better growth and vigor, indicating that vitamin C plays a part in the physiology of the animal even of a species which does not develop scurvy symptoms. The improvement in growth and vigor thus observed to result from the addition of orange juice (rich in C vitamin) to the diet of an animal not showing typical symptoms of scurvy, finds its parallel in human experience in the clinical observations of Hess, who found many cases of subacute or latent scurvy among infants. These cases do not show pronounced scurvy symptoms but are irritable, lacking in stamina, and more or less retarded in growth. Better growth, higher stamina, and better general health and disposition are induced by the feeding of vitamin C in the form of orange or tomato juice or other suitable antiscorbutic food.

McCarrison found (122) that in guinea pigs rendered scorbutic by diet deficient in vitamin C the adrenal glands are enlarged and congested, and that this hypertrophy of the adrenals is associated with diminished production of adrenalin, which may readily be a factor in the hemorrhages so characteristic of scurvy. Conversely, this suggests the possibility of vitamin C playing a part in normal physiological processes through its apparent relation to adrenalin production.

Zilva and Wells (230) have reported changes in the teeth of scorbutic animals even before the appearance of the usual scurvy symptoms. They find that the tooth is one of the first if not the first part of the body to be affected by a deficiency of vitamin C and that the teeth may be seriously affected, even when scorbutic symptoms are so slight as to be almost unrecognizable. Applying their observations to human nutrition, these authors suggest that the use of food poor in vitamin C may be an important factor in the great prevalence of tooth decay in civilized communities, since cases of incipient scurvy so mild as to escape detection may occur more often than is usually supposed and may reasonably be expected to influence dentition. See also the work of Howe (108), (109).

Drummond's above-mentioned experiments, in which vitamin C in the form of orange juice was added to the diets of rats, were continued into the second generation and it was found that a larger number of litters of young were borne by the females which received the added antiscorbutic—a finding which has been confirmed by most but not all of some similar comparisons made in the writer's laboratory.

Drummond concludes that although the need of the rat for vitamin C is relatively much less than that of man, the monkey or the guinea pig, yet it is sufficiently well-marked to dispel any idea that there exists a fundamental difference in the nutritive requirements of the two types of animals. "It may therefore be accepted as experimentally proven that the dietary requirements of the higher animals include in addition to a satisfactorily balanced ration of protein, fat, carbohydrate and mineral salts, an adequate supply of three accessory food factors: Fat-Soluble A, Water-Soluble B or antineuritic factor, and Water-Soluble C or antiscorbutic factor." That the antiscorbutic vitamin is a factor in the normal nutrition even of the rat is strikingly indicated by the recently published observation of Parsons (177) that rats' livers contain antiscorbutic vitamin even though the animals have been fed for a long time on a diet supposedly devoid of it. As Parsons points out, it seems improbable that the presence of vitamin

C in the livers of the rats under such conditions should be accidental. Other possible explanations are that the rat may be able to synthesize this vitamin, or that the vitamin may exist, in cereal grains for instance (the diet fed by Parsons to these rats contained 64 per cent of wheat), in a modified form utilizable by the rat but not by the guinea pig, or that the autiscorbutic requirement of the rat may be so much smaller than that of the guinea pig that a small amount of vitamin C present in the wheat of the experimental ration, while so far insufficient for the guinea pig as to be unrecognizable by guinea pig feeding tests might yet suffice to meet the needs of the rat and enable it to carry some store in the liver. "It is conceivable that the rat has acquired not only a lowered requirement but also a phenomenal capacity to store the antiscorbutic substance through a biological adaptation to a food supply which over long periods of time is very deficient in this substance." In the same paper mention is made of preliminary experiments comparing the vitamin C content of eggs and newly hatched chickens which "appear to give additional weight to the probability of a synthesis of antiscorbutic substance by certain animal tissues, or a utilization of forms other than those available to the guinea pig" (177, p. 602).

Distribution of vitamin C in the body and in foods. In the experiments of Parsons just cited, as well as in other investigations, it has been made clear that the liver may be much richer in vitamin C than the muscles. In fact the muscles even when tested fresh and raw show barely demonstrable antiscorbutic effects. Thus the ordinary meats are very low in antiscorbutic value. Several investigators report entirely negative results when testing meats for antiscorbutic vitamin, but human experience appears to demonstrate that fresh meat in liberal amounts may exert a slight antiscorbutic effect. Blood appears to contain distinctly more of the antiscorbutic vitamin than does muscle, and it is due in part to their preference for blood and the glandular organs rather than the muscles as food that the carnivora obtain a sufficient amount of vitamin C from their prey.

Milk is much richer than muscle in its content of antiscorbutic vitamin, but is subject to considerable variation in this respect according to the antiscorbutic value of the food consumed during lactation. The milk of cows on fresh pasture has been found to be at least three times as rich in antiscorbutic vitamin as is that of cows fed on an extremely scorbutic winter ration (3), (18), (49), (87), (98), and it is probable that similar differences may occur in breast milk according as the food of the mother is rich or poor in antiscorbutics.

Among foods of vegetable origin, fruits and succulent vegetables are the most important sources of vitamin C (15), (27), (90), (93), (106). Oranges (74), lemons (82), tomatoes (73), and fresh raw cabbage (28) seem to be the richest in antiscorbutic vitamin of the foods thus far studied. Apples, bananas and especially potatoes (75), while not so rich in the vitamin, are yet very important antiscorbutics because of the quantities in which they often enter into the diet.

In general green vegetables such as leaves, growing shoots, the edible immature seedpod of the "snap," "string" or "runner" bean (11), (28), (30), (106), when eaten fresh and raw or nearly so, are rich in vitamin C, ranking with fruits as antiscorbutics; while root vegetables in general contain a somewhat lower concentration of the antiscorbutic vitamin (20), and mature seeds are almost if not entirely devoid of antiscorbutic properties.

It is to be mentioned, however, that in any such simple grouping there may be considerable variations within any one group, and this is not to be avoided by a more elaborate subdivision of plant products according to biological classification or general chemical composition, since in some cases foods very similar from either of these points of view appear to have quite different antiscorbutic values. Thus the juice of the lemon has shown much higher antiscorbutic value than that of the lime (19) and the Swedish turnip is reported to be much richer in vitamin C than the common white turnip (20). In how far such differences are to be regarded as fixed for the species and varieties concerned and in how far they may have been due to difference in soil, climate, season, handling or storage of the particular specimens used in the feeding experiments reported, or even to the technique of the experiments and the individual variability of the experimental animals employed, it would at present be exceedingly difficult and probably impossible to decide.

Undoubtedly a marked development of antiscorbutic vitamin occurs in cereal or legume seeds as they germinate. Sound mature legumes and cereals as well as the mill products and breadstuffs made from them are commonly regarded as devoid of antiscorbutic property, while properly germinated pulses and malted grains rank as valuable antiscorbutics (14), (101), (224). Hence there must occur in the germinating seed either a formation of vitamin C or a change from an inactive to an active form. Since the string bean, with its immature seed and the fleshy pod which feeds it, is fairly rich in antiscorbutic, there is here plainly a suggestion that as the seed matures and goes into a resting

stage the antiscorbutic vitamin goes into an inactive form or a related but inactive substance from which it is regenerated when the seed germinates. It will therefore be of theoretical as well as practical interest to test green peas fresh from the garden, and fresh green corn in the immature state at which it is eaten as a "vegetable," for antiscorbutic properties.

In this connection it will also be of interest and importance to determine whether the soaking of seeds to such an extent as sometimes precedes the application of heat in cookery may result in the development of any appreciable antiscorbutic power. There seems to have been an indication, but as yet no conclusive proof, of slight antiscorbutic effects from legumes which have been soaked but not sprouted. And among the Russian peasants there is a belief that their black bread, prepared from whole grain flour (including the embryo) by a slow process in which there are both a long soaking and an opportunity for considerable enzyme action to take place, has some value as an antiscorbutic while white bread, made from the endosperm only and by a quicker process, has none. Another important problem relates to the preservation of the antiscorbutic values of such foods as are commonly used fresh but cannot always be had in fresh form. Exclusive of the development of antiscorbutic vitamin in seeds by soaking and germination, any given food may be expected to show its maximum antiscorbutic value in its perfectly fresh raw state. But what is more important is to realize that some foods can be preserved almost indefinitely with little if any diminution of antiscorbutic value while of others this can not be expected.

It is unsafe to generalize from the method of preservation alone, as for example to attempt a general answer to the question whether a sufficient supply of antiscorbutic vitamin can be obtained from canned food. Canned meat is practically devoid of antiscorbutic value, while canned tomato is one of the best of the antiscorbutics known (90), (115). There are at least three reasons for the great difference in this respect between canned meat and the canned tomato: (*a*) the initial concentration of vitamin C is much higher in the tomato than in the meat; (*b*), the acidity of the tomato tends to prevent the destruction of its vitamin both during the canning process and subsequently in storage; and (*c*), partly because of this acidity much less drastic heat treatment is employed in the canning of tomatoes than in the canning of meats.

Canned milks differ greatly as regards their antiscorbutic value, not only because the concentration of vitamin C in the original milk is subject to variation with the feeding of the cow, as above mentioned, but also because the canning process involves very different heat treatment in different cases. Unsweetened canned milk (the "evaporated" milk of commerce) depends for its preservation upon concentration and heat treatment only and is given such thorough heating to ensure against subsequent spoilage that the antiscorbutic vitamin is apt to be almost entirely destroyed (89). On the other hand milk canned with sugar (commonly called sweetened condensed, or commercially simply "condensed" milk) is preserved in large measure by the sugar present as well as by the concentration of the milk solids, and therefore needs less heat treatment. Such condensed milk Hess finds "to retain the larger part of its antiscorbutic factor" (91), and it has also been found to contain important amounts of antiscorbutic vitamin by other recent investigators (110).

Foods of high initial acidity such as tomatoes and orange and lemon juice can be dried and still retain marked antiscorbutic value (73), (74), (75), while attempts to conserve the vitamin C during the drying of less acid foods such as cabbage (30) and potatoes (75) have been less successful. The drying of milk is perhaps more highly developed from the mechanical standpoint than that of any other food, and since it is nearly neutral in reaction and largely used in infant feeding, special interest attaches to the question of retention of the antiscorbutic value of milk during its drying. Some tests of dried milk have shown antiscorbutic value and others have not (3), (88), (90), (112). The tendency has been to ascribe the difference to the mechanical process used in drying, but in view of the fact that the initial concentration of vitamin C in milk is now known to vary rather widely, and the further fact that the mechanical devices for the drying of milk are undergoing still further development, it is doubtful if the differences reported should be attributed to the mechanical process alone. The time and temperature of heating to which the milk is subjected in drying depend not only upon the mechanical principle of the process but also upon the manner in which it is carried out.

For the solution of questions arising when one attempts to investigate moderate quantitative changes in the antiscorbutic value of a food, special refinement of experimental method becomes necessary.

Quantitative determination of the antiscorbutic vitamin. Holst and Fröhlich (100), (101) made comparisons of the antiscorbutic properties

of different foods and of the same food before and after cooking, drying or other treatment, by finding the quantities which when fed daily to a guinea pig as his sole source of antiscorbutic would suffice to protect him from scurvy. The weakness of their method consists in the fact that they were not dealing with a deficiency of the C vitamin alone since the simple basal rations which they employed—usually grain and water only—must have been deficient in vitamin A and calcium as well.

Cohen and Mendel (21) devised a new basal ration planned to provide all necessary nutrients except the antiscorbutic; showed that the condition of experimental scurvy can be induced in the guinea pig at will; and formulated more fully the criteria for the recognition of this condition.

Chick and Hume (15), (17), (18), (19), Delf (28), (29) and other workers at the Lister Institute have done much to establish the importance of quantitative methods of work in the study of antiscorbutic values, and have recorded minimum protective doses of different foods and of the same food under different treatments, as determined by experiments upon guinea pigs fed a basal ration of oats, bran and autoclaved milk. In view of the more recent investigation mentioned below (115), it is doubtful if the heat treatment to which they subjected milk can be depended upon to have certainly destroyed all of the vitamin C and still retained an adequate amount of vitamin A. Using a liberal amount of autoclaved milk in order to ensure enough of the A vitamin, it is probable that their basal ration contained a very small but somewhat variable amount of vitamin C.

La Mer, Campbell and Sherman (115), building upon the experience of Cohen and Mendel and of Chick, Hume and Delf, have still further developed the basal ration so as to ensure its freedom from vitamin C and its entire adequacy in all other respects, and have further standardized the method with reference to the age and size of the guinea pigs used and the calculation of the dosage of antiscorbutic to a definite basis of guinea pig weight. With the various factors thus standardized it was found possible to measure relative antiscorbutic values not only by the method of finding the minimum dosage required for complete protection from scurvy, but also by means of a system of quantitative rating of the severity of the symptoms and autopsy findings in experimental animals receiving accurately measured amounts of the food to be tested, which amounts prove to be below the dosage required for complete protection. Applying this method repeatedly

in studies of the heat destruction of the vitamin, it was found that measurements of the relative amounts of vitamin present can thus be made with a probable error of less than 5 per cent.

Physical and chemical properties of vitamin C: Its destruction by heating and oxidation. Holst and Fröhlich (100), (101) and their coworkers showed that the antiscorbutic substance is readily soluble in water, dialyzable, organic, not volatile but rather readily destroyed by heat, especially as it occurs in foods which are not naturally acid. Cohen and Mendel (21) and Hess and Unger (93), (94) confirmed and extended these observations and established the actual existence of an antiscorbutic substance as against the view that antiscorbutic effects might be referred to the physical properties of the food. Hess (94), (95), (96) as well as Harden (79) demonstrated the susceptibility of the antiscorbutic vitamin to alkalinity and Delf (28), (29) made approximately quantitative studies of the influence of temperature upon the rate of destruction of vitamin C in cabbage at its natural hydrogen ion concentration.

La Mer, Campbell and Sherman (115), using the method above mentioned for the quantitative determination of the vitamin, studied the effect of temperature and of hydrogen ion concentration upon the rate of its destruction in solution.

In the case of tomato juice of natural acidity, pH = 4.3, it was found that boiling for one hour destroyed practically 50 per cent, and for four hours practically 68 per cent, of the antiscorbutic vitamin present. The time curve of the destructive process is therefore much flatter than that of a unimolecular reaction. The latter finding applies also to similar heating experiments at 60°C. and at 80°C. In such experiments at 60° to 100° the temperature coefficients are relatively low: Q_{10} (60°–80°) = 1.23; Q_{10} (80°–100°) = 1.12.

In experiments in which the natural acidity was first neutralized in whole or in part, the juice then boiled for one hour and immediately cooled and reacidified, it was found that at pH = 5.1 to 4.9 (natural acidity less than half neutralized) the destruction during one hour's boiling was increased to 58 per cent. Neutralization of a larger proportion of the natural acidity increased the rate of destruction of the vitamin at 100°. When alkali was added to an initial pH of 11, which fell to about 9 during the hour of heating, the destruction found on feeding of the juice thus treated but immediately cooled and reacidified was about 65 per cent.

When in experiments, otherwise exactly like the ones last mentioned, the solutions after heating were quickly cooled and stored without reacidification for from one to five days in the refrigerator before feeding the destruction found was 90 to 95 per cent, thus showing the marked deleterious influence of the alkali upon the vitamin on standing even at great dilution and at the low temperature of the ice box.

In these experiments the solutions were heated in cotton-stoppered, narrow-necked flasks from which the air must have been very nearly excluded by water vapor early in the heating, so that the effects noted are essentially those of heating rather than of oxidation, although the latter may not have been entirely excluded. In similar experiments in which oxygen or hydrogen was bubbled through the solutions during the heating it was found that the presence of oxygen increased the rate of destruction of the C vitamin. Zilva (228) has reported destruction of vitamin C in neutralized lemon juice when boiled for two hours with air bubbling through the container, while in similar experiments in which CO_2 was bubbled through the flask no destruction of the vitamin was apparent.

Hess and Unger (99), Dutcher (1) and others have already demonstrated the marked susceptibility of this vitamin to such drastic oxidizing conditions as are involved in treating the solution containing the vitamin with liberal amounts of hydrogen peroxide.

Thus while the instability of vitamin C makes it an unpromising material for attempts at actual isolation, the development of methods for its quantitative measurement is making possible a systematic study of its chemical behavior.

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PHYSIOLOGICAL EFFECTS OF ALTITUDE

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Altitude is a climatic condition that causes physiological changes which affect our bodily comforts. Among its variables are lowered atmospheric pressure, partial pressure of oxygen, temperature and humidity; and increased intensity of sunshine and electrical conditions. While in the past the effects of altitude have been attributed to one or more of these variables (15), (37), (104), it is today recognized that the controlling element in the physiological reactions is the diminished partial pressure of oxygen and the consequent imperfect aeration of the arterial blood.

The altitude oxygen want is ascribed to two conditions. Primarily it is due to the imperfect saturation of the arterial blood with oxygen, which is the result of reduced atmospheric pressure; but secondarily it becomes temporarily more pronounced because of a chemical change in the blood that prevents as free a passage of oxygen into the tissues as is normally the case. This oxygen want may cause trouble in the body which is usually soon offset by compensatory reactions that ultimately, if a residence be maintained, lead to acclimatization. The anoxemia, defined (45) as a condition in which the rate of supply of oxygen to the tissues is insufficient, means in many men a temporary slowing down of life.

Barcroft (6) has pointed out that acute anoxemia simulates drunkenness; while chronic anoxemia, which is an oxygen want, perhaps not very great but that may be continued over months, simulates fatigue. He classifies the chronic types of anoxemia as the anoxic, anemic and stagnant. In the first the pressure of oxygen in the blood is too low and the hemoglobin is not saturated to the normal extent; in the second the quantity of hemoglobin in the body is too small, but the oxygen pressure is normal; in the third the blood is normal, but supplied to the tissues in insufficient quantities. It is the anoxic type that occurs at high altitudes and this, according to Barcroft, is the most difficult for the organism to circumvent, since the rate of delivery of oxygen to the tissues depends upon the pressure of oxygen in the blood.

The behavior of the organism under low oxygen depends upon four factors: *1*, the suddenness with which the oxygen is decreased; *2*, the extent to which it is decreased; *3*, the length of time it is decreased; and *4*, to some extent, upon the physical condition of the body. These should be recognized in any statement of symptoms of and compensations to altitude. Thus the conscious and outwardly appearing reactions experienced by the aviator and the mountaineer are, as a rule, quite unlike because of the speed as well as the extent of oxygen reduction. The compensations to altitude fall into two categories: namely, the emergency adjustments based upon temporary functional changes; and the permanent which, by profound alterations, result in acclimatization. The lowest altitude at which the temporary compensations occur will depend to a considerable extent upon the speed with which the ascent is made and the degree of response upon the height reached. The permanent adjustments require time and their onset and amount will be determined by the first two factors.

The ability to compensate to the low oxygen tensions of high altitudes varies with the individual and the adjustments may be more rapid and effective at one time than another. In repeated journeys to the summit of Pike's Peak the author has experienced several degrees of mountain sickness and at other times has escaped the malady. In the U. S. Army Air Service (2), (3), (68) the experience with the altitude classification test of low oxygen by rebreathing, has shown that men, who ordinarily compensate well to the low oxygen, may pass through a period in which they do poorly. While the differences cannot be entirely accounted for, yet without doubt they have many times been associated with health.

Much of our information regarding the effects of altitude has been obtained by methods of investigation that did not necessitate living on the mountains. Various researches (10) have shown that merely to subject the organism to a deficiency of oxygen calls forth the reactions characteristic of altitude. Lutz and Schneider (66) subjected men to low oxygen tensions produced in three ways: by low barometric pressure in a low pressure chamber, which was continuously supplied with fresh air; by a low percentage of oxygen caused by rebreathing air confined to a mechanism in which the normal atmospheric pressure was maintained and from which the carbon dioxide was removed; and by diluting the respired air with increasing amounts of nitrogen. By conducting experiments more or less parallel as to time, rate and duration, they were able to prove that the circulatory, respiratory and

blood adaptive changes were practically identical in these three methods.

A study of altitude and anoxemia leads to the conclusion that much work has been partially or wholly futile because of unsatisfactory experimental methods. This lack has given a literature full of contradictory theories and conclusions. The space allotted by the editors of this journal makes it impossible to consider many interesting studies. Only such as bear on recent work will be considered. The reader is referred to Cohnheim (17) and Zuntz, Loewy, Müllar and Caspari (104) for helpful reviews of many topics.

Attention is called to the fact that expeditions have many times been made to altitudes that were too low to give a satisfactory response, and the time spent at the altitudes has often been too short for the adaptive changes to have progressed sufficiently to be measured. The process of acclimatization has been studied for altitudes only up to 15,000 feet. The most satisfactory returns have come from expeditions made to 14,000 feet or higher. The results obtained by a short sojourn at 6000 to 10,000 feet have been, as a rule, unsatisfactory. Our knowledge of more acute oxygen want, as experienced in flying, includes altitudes up to those that cause unconsciousness.

The responses of the organism to the anoxemia of altitude involve the respiration, blood and circulation, and are: *1*, a fall in the alveolar carbon dioxide pressure and a rise in the alveolar oxygen pressure, which are associated with an increase in the ventilation of the lungs; *2*, an increase in the percentage and the total amount of hemoglobin in the blood; *3*, a modification in the proportion of acids and bases in the blood; and *4*, an increase in the rate of heart beat, with which are also associated other circulatory changes. Each of these has been considered to be in the nature of a compensation, so that the tissues may be more adequately supplied with oxygen. The respiratory changes raise the oxygen pressure to which the blood is exposed; the increase in hemoglobin provides for more oxygen in a given unit volume of blood; the chemical changes provide the conditions for an adequate dissociation of oxyhemoglobin in the tissue capillaries; and it has been thought that the circulatory changes result in an increased volume of blood flow, which would raise, to a slight extent, the oxygen pressure in the tissues.

It has been found that under the conditions of flying the respiration and circulation are the first mechanisms to be stimulated, and they are almost equally sensitive to relatively low altitudes; while at higher

altitudes the blood may also concentrate (42). During residence at a high altitude, the respiration is the first function affected and may even begin to change during the ascent. Ordinarily in the mountaineer the beginnings of the blood and circulatory changes are delayed by at least as much as 6 to 24 hours. There is evidence that the most temporary of the several changes are those affecting the circulatory system. In the interactions of the several physiologic functions concerned in acclimatization, the circulation alone tends to return to the low altitude normal; while the other functions continue on at the new levels as long as residence at the altitude is maintained.

SYMPTOMS NOTICEABLE AT HIGH ALTITUDES. When anoxemia is produced gradually and rapidly as in an airplane ascent the effects are insidious and easily overlooked. In fact many aviators find it difficult to analyze their sensations and are not sure that altitudes produced any effect. This is because the most striking action is on the nervous system. The first effect is stimulation and results in a feeling of well-being, but this stage gradually and insensibly passes into sensory and mental dullness (3), (4), (12), (65). At 12,000 feet the aviator may be conscious of breathlessness, a little higher he feels muscular weakness when moving, there may be a headache and a tendency to Cheyne-Stokes breathing. As he continues to ascend memory and judgment are gradually impaired, while sight and hearing become dulled. Many men experience an overpowering desire to sleep, while fainting is not uncommon. Unfortunately the aviator often becomes possessed with fixed ideas and being unable to reason does foolish things. To then continue to ascend means loss of consciousness. Between 23,000 and 25,000 feet appears to be the upper altitude limit for consciousness for unacclimatized men.

There are after-effects of an altitude flight that are of special interest, such as unusual fatigue, subnormal breathing in which the rate and depth are decreased, subnormal blood pressure and headache.

The mountaineer ascends more slowly and, unlike the aviator, is liable to an attack of "mountain sickness." The first effect as in a rapid ascent is stimulating. When the traveller arrives at the summit of a mountain such as Pike's Peak, altitude 14,110 feet, he may feel unusually well and exhilarated, often showing a disposition to be talkative, unreasonable or quarrelsome. His lips are blue, he is unusually sensitive to cold, feels light-headed and may have a headache. As the day passes, in 6 or 8 hours, lassitude is felt; the headache, which is frontal, gets worse; the appetite fails; there is likely to be nausea

and vomiting; and frequently there is a sense of oppression in the chest and a rapid pulse. There is always depression, more or less muscular weakness, and sometimes complete prostration. The next morning the eyes are dull and heavy, temperature subnormal, the tongue furred, and the bowels disturbed. This condition may last a day or two and if the patient remain quiet the attack is soon over. Strauch (88), having reviewed the mountain sickness experiences of early explorers, calls attention to the fact that this malady befalls some individuals at a lower, others at a higher altitude; but that for all there is a critical line beyond which escape is impossible. In some it may occur at 10,000 feet, while only a very few can venture to 19,000 feet without the experience.

Ravenhill (75) who had a large experience among the Andes Mountain mining camps at 15,400 feet describes, in addition, a cardiac and a nervous type of mountain sickness:—the former is characterized by acute heart failure and the latter by persistent vertigo, trembling and even convulsions.

THE RESPIRATION AT HIGH ALTITUDES. The early observations on the influence of altitude on respiration dealt mostly with the rate, depth and per-minute volume of breathing and have shown that the amount of change varies with individuals (26), (36), (70), (104). Altitudes up to 15,000 feet either slightly increased or decreased the rate of breathing; the depth of breathing as a rule was increased although in some men the opposite resulted; and the per-minute volume of breathing was found to be increased, but when corrections were made for temperature and pressure by reducing the volume to 0°C. and 760 mm. the volume of breathing at 15,000 feet was from 10 to 78 per cent less than at low altitudes.

Altitude and other types of low oxygen studies have thrown much light on the method of control of respiration. To Haldane is due the credit of initiating the study which has given not only the facts but also very largely our present day interpretations. At low altitudes a close relationship exists between the alveolar tension of carbon dioxide and the per-minute volume of breathing; the two vary proportionately, but the carbon dioxide tension remains rather constant. However, at high altitudes the opposite relationship obtains, the alveolar carbon dioxide is decreased while the breathing is increased. This difference is based upon blood changes. The alveolar air changes in carbon dioxide and oxygen can be used to determine just when and to what degree the respiration responds to altitude. Zuntz and

co-workers (104) and Durig's (26) Monte-Rosa Expedition in 1906 determined, by indirect methods, that the alveolar carbon dioxide is lowered as the barometric pressure falls; but it required the more exact and direct method of Haldane and Priestley (47) to follow the changes in detail. The direct method was early applied by Boycott and Haldane (14) in a low pressure steel chamber, and later by Ward (98) on Monte Rosa, and by the Anglo-American Expedition (23) on Pike's Peak.

The members of the Anglo-American Expedition at 14,110 feet already showed a fall in the alveolar carbon dioxide when the first analysis was made in from 30 to 60 minutes after arrival on the summit. This indicates that the respiratory response began during the journey up the mountain. However, the process was then by no means completed. The average CO_2 tension upon arrival was 32.8 mm.; this was followed by a gradual fall for from 3 to 19 days when it went to between 25.4 and 29.5 mm. In all cases the alveolar tension of oxygen was of course least the first day or so, ranging from 40.2 to 47.1 mm.; and then gradually rose as the CO_2 tension fell, reaching finally from 54 to 56.4 mm. This rise in alveolar oxygen pressure is one of the important events of acclimatization. Had the sea level CO_2-tension of 40 mm. been maintained at 14,110 feet, the alveolar oxygen pressure would have been only 36 mm. The new regulation gradually raised the alveolar oxygen pressure a little more than 16 mm. above what it would otherwise have been.

A fall in the alveolar CO_2-tension indicates an increase in the per-minute volume of breathing. The Anglo-American Expedition found that one individual breathed per minute in bed at sea level 7.7 liters; and when acclimated at 14,110 feet, 10.2 liters; when standing at rest at sea level 10.4 liters, and at 14,110 feet, 14.9 liters.

Miss Fitzgerald (32), (33), from a study of acclimated inhabitants at many altitudes found that the alveolar CO_2-pressure diminishes as altitude increases. She formulated the law that for every fall of 100 mm. in the barometric pressure there is approximately a fall of 4.2 mm. in the alveolar carbon dioxide pressure. This means that approximately a 15 per cent increase in the ventilation of the lungs occurs for each 5,000 feet increase in altitude.

During rest, in the acclimatized person, the breathing is ordinarily modified only in depth. During physical exertion the rate increases more rapidly than in the same exercise at sea level. Thus one subject when standing at sea level breathed 17 times per minute, on Pike's

Peak 20 times; walking at the rate of 4 miles per hour at sea level 17.2, on Pike's Peak 29 times; and at the rate of 5 miles per hour at sea level 20, and on Pike's Peak 36 breaths per minute. The increase in the volume of breathing for the same conditions were: standing at rest at sea level 10.4, on Pike's Peak 14.9 liters; walking at 4 miles per hour at sea level 37.3, on Pike's Peak 57.0 liters; walking at 5 miles an hour at sea level 60.9, and on Pike's Peak 110.2 liters per minute. These figures make it clear that excessive hyperpnea is experienced on exertion during a sojourn at 14,000 feet, but this becomes less marked after the first day or two.

The consumption of oxygen during such exertions is approximately the same for each degree of effort at sea level and the high altitude. Most of the investigations show that metabolism is independent of variations in barometric pressure (23), (27), (28), (36), (53), (92), (104).

By means of experiments conducted in a low pressure steel chamber and by low percentages of oxygen at normal atmospheric pressure, Lutz and Schneider (66) have attempted to simulate the rate of ascent of an aviator to 18,000 or 20,000 feet. The alveolar CO_2-pressure and the per-minute volume of breathing were found to be changed at 656 mm. barometric pressure (4000 feet). Ellis (30) by the re-breathing method secured as early a response. It appears then that the respiratory response of increased breathing is stimulated almost at once by altitude during flying. The alveolar carbon dioxide and oxygen tensions fall progressively during an ascent to 20,000 feet, the carbon dioxide from an average of 39.7 to 30 mm., and the oxygen from an average of 103.2 to 34.8 mm. The oxygen pressure in the blood as it leaves the lungs would average, according to Barcroft (6), 5 mm. less than the alveolar oxygen pressure. So we have in the alveolar oxygen pressure, by referring to the normal dissociation curve, a measure of the degree of saturation of the arterial blood with oxygen and, therefore, of the degree of anoxemia.

In an ascent of short duration, such as an airplane flight, if a high level be maintained for an hour or more there is a tendency for the alveolar carbon dioxide tension to rise somewhat and the per-minute volume of breathing to decrease toward normal. Ellis (30) and Lutz and Schneider (66) correlate these changes with the appearance of other compensations to low oxygen that are advantageous to the subject; while Haldane, Kellas and Kennaway (49) attribute this falling off in the breathing to a washing out of preformed CO_2 from the blood by the increased breathing.

The after-effects on the respiration of a stay at a high altitude of 1 or 2 hours are of short duration. Lutz and Schneider with low pressure chamber experiments found that, in a stay of from 30 to 90 minutes at a pressure corresponding to 15,000 feet, in 4 out of 5 subjects the alveolar air CO_2 was back to normal within 20 minutes after returning to 760 mm.; while in only 4 out of 9 cases was the return made in the same time after a stay at 18,000 feet. It has been a common observation among aviators that breathing is subnormal for awhile after landing. In that time the organism is making up the loss in CO_2 and recalling alkali into the blood. There is evidence that relatively permanent factors of adaptation soon begin to relieve the more temporary compensations. Thus Boycott and Haldane (14) report a case held 24 hours at 545 mm. in a low pressure chamber in which the alveolar CO_2-pressure had scarcely returned to normal after 2 days. The persistence of the after-effects has been noted after residence on a mountain by Ward (98) and by the Anglo-American Expedition (23). The most conspicuous case was reported by Schneider (78) for a man who had lived 6 months on the summit of Pike's Peak. This man continued to show a hyperpnea for at least 4 weeks, in which time his alveolar CO_2-tension gradually rose from 27.1 to 37 mm. While the aviator breathes subnormally, the mountaineer ventilates his lungs excessively during the period of "after-effect." The former has an alkalosis of the blood and the latter a high ratio of fixed acids to bases. The mountaineer very likely is slowly accumulating blood alkalies and increasing the blood content of volatile acids.

Periodic breathing is frequently observed among newcomers at very high latitudes. This was first observed by Mosso (70), and later studied by Douglas (21) and by the Anglo-American Expedition. It no doubt is caused by want of oxygen, in that it has been abolished by the administration of pure oxygen.

Vital capacity. Authorities agree that a decrease in the vital capacity takes place with a lowered barometric pressure, but the explanations as to cause differ. Zuntz and co-workers (104) explain this change as being due to the expansion of intestinal gases. Durig (26) leans toward fatigue of the respiratory muscles as the true explanation. Fuchs (36) finds cause in an increase of muscle tone due to low temperatures. Durig and Zuntz (27) later accept in part this viewpoint. Experiments in low pressure chambers give a similar reduction. Schneider (68) by this means has shown that the breathing of oxygen prevents a part of the decrease.

Oxygen secretion by the lungs. Opinion has been divided as to the means by which the passage of oxygen into the blood is effected at high altitudes. One group, the larger, has maintained that both at low and high altitudes the oxygen enters the blood solely by diffusion through the pulmonary epithelium; whereas the other group has maintained that diffusion alone cannot account for the intake of oxygen, but that it is supplemented by an active secretion of oxygen by the pulmonary epithelium. The secretory theory has received its support from observations of the Anglo-American Pike's Peak Expedition. It is admitted that, if the oxygen pressure in the blood be higher than in the alveolar air, only the secretory theory will account for this difference. In order to measure the partial pressure of oxygen in the blood of men on Pike's Peak, Douglas, Haldane, Henderson and Schneider (23) used the indirect method of Haldane and Smith (46), as modified by Douglas and Haldane (22), in which the administration of carbon monoxide and the law of mass action are employed to determine the partial pressure of oxygen. By this means they found the average excess of oxygen pressure in the arterial blood was 35.8 mm., the mean normal resting alveolar oxygen pressure 52.5, and the arterial pressure 88.3 mm. They also used the then known facts regarding diffusion of oxygen and found that alveolar oxygen pressure at that altitude would not deliver oxygen to the blood rapidly enough to supply the bodily needs, especially during exercise. Today it appears that these results and conclusions were based on untrustworthy assumptions. Dr. Marie Krogh (60) in 1915 established a new diffusion-coefficient for the passage of oxygen through a membrane and showed that, if the figures were correct, it was possible for diffusion to account for the passage of a sufficient amount of oxygen to supply the body needs up to such altitudes as 24,000 feet. The theory so far as altitudes are concerned was from then on only supported by the indirect evidence that the oxygen pressure in the arterial blood was higher than in the alveolar air. More recently Barcroft, Cooke, Hartridge and Parsons (9) drew blood directly from the radial artery of the wrist of a man who had lived 6 days under an oxygen pressure of 84 mm. By carefully controlled methods the oxygen pressure of the blood was determined by two direct methods of measurement, the blood-gas pump and the differential blood-gas apparatus. They conclude that "The arterial blood *in vivo* contained less oxygen both during rest and work than did samples of the same blood exposed to alveolar air *in vitro* at body temperature." So for the present it appears that the burden

of proof for the theory of oxygen secretion by the lungs lies with its advocates.

THE BLOOD CHANGES. The extensive literature on the blood is discordant, some maintaining that altitude is entirely devoid of effect and others insisting that extreme changes occur. This lack of agreement is most conspicuous regarding the changes in the number of red blood cells. A good review of the early literature is given by Bürker, Jooss, Moll and Neumann (15). Their work emphasizes the necessity of employing experimental methods of a high degree of accuracy.

Erythrocytes and hemoglobin. As early as 1878 Paul Bert (10) predicted that the blood of man and animals living at high elevations would be found to have a greater oxygen capacity than that of similar individuals at sea level. In 1882 (11) he showed that the blood obtained from several kinds of animals living at a high altitude in Bolivia had a greater oxygen capacity than that taken from animals at sea level. A little later, in 1890, Viault (95) reported an increase in the number of red corpuscles per cubic millimeter of blood in man and animals at an elevation of 14,400 feet in Peru; while Müntz (72) found that the blood of animals, living at an altitude of 9400 feet in the Pyrenees, contained a larger percentage of iron than that of those at low levels.

While these early observations have from time to time been controverted, at the present time the evidence for an increase in the erythrocytes and hemoglobin is overwhelming.

The relation between the increase in the number of erythrocytes and amount of hemoglobin has also been a subject of debate. Schaumann and Rosenqvist (77), Oliver (73), VanVoornveld (96) and Fuchs (35) found that the increase in red cells exceeded that of hemoglobin, while Eggers (29) and Dallwig, Kolls and Loevenhart (20) report a much smaller increase in red cells than in hemoglobin. The Anglo-American Pike's Peak (23) expedition in 1911 found the red corpuscles to increase in equal proportion with the hemoglobin, so that there was no alteration of the color index. Bürker (15) and collaborators at 6150 feet found the erythrocytes to increase 4 to 11.5 per cent and the hemoglobin 7 to 10 per cent. Cohnheim (18) and Schneider and Havens (82) find the two changes run parallel. It is to be expected that as more exact methods of determining the hemoglobin come into use, it will be shown that the color index is not changed with altitude.

If the increase in erythrocytes and hemoglobin prove to be parallel, then Miss Fitzgerald's (32) law may be accepted as a measure of these

blood changes. She found that for every 100 mm. fall in atmospheric pressure there is, among acclimated inhabitants, an average rise of about 10 per cent in hemoglobin and that this rise is approximately the same for men and women.

The aviator and balloonist may also experience blood compensations. Studies during a flight are difficult to make and subject to the criticism that the wind causes such rapid evaporation of the freshly drawn blood that an increased count may be attributed to its action. Gaule (39), Gemelli (40) and Culpepper (19) report increases in the erythrocytes and hemoglobin during flights; and the last two authorities hold that repeated ascents will give a permanent increase. They advance the opinion that cold is the main cause. A rapid increase in the absence of cold has been demonstrated by means of the low pressure chamber and under low oxygen at normal atmospheric pressure by Gregg, Lutz and Schneider (42). They and Haldane, Kellas and Kennaway (49) fail to find a lasting effect from brief exposure to low oxygen tensions.

Rate and time of change. To determine the rate at which these blood changes take place during residence at a high altitude necessitates making allowance for the diurnal variations. Dreyer, Bazett and Pierce (25) have shown that the daily variations in the per cent of hemoglobin in man and animals are large, changes of 10 per cent are more or less common and may even reach as much as 30 per cent. The diurnal curve shows two maxima between 4 and 8 a. m. and p.m. and two minima between 10 and 1 o'clock night and day. If the literature on altitude blood changes be examined with this curve some of the disagreement between investigators can be accounted for.

The time required for the altitude blood changes to become evident appears to be determined by the rate and height of the ascent and the physical condition of the subject and, to some extent, by the amount of physical effort made. Gregg, Lutz and Schneider (42) with the low pressure chamber and low oxygen at normal atmospheric pressure observed that, when the oxygen tension was lowered at a rate comparable to ascending 1000 feet per minute, to pressures corresponding to 15,000 to 18,000 feet, the erythrocytes and hemoglobin increased in 78 per cent of all men examined. In some of the men the increase began within 26 minutes and in the majority between 40 and 60 minutes.

The mountaineer, whether going afoot, by railway or automobile, ascends more slowly than the aviator; consequently the blood changes appear much later. Douglas, Haldane, Henderson and Schneider (23) observed in themselves, several hours after reaching the summit of

Pike's Peak, a slight increase in hemoglobin that did not reach 3 per cent in any case. Work with animals has revealed an increase within a few hours (16), (20). Schneider and Havens (82) had under observation healthy young men who ascended passively by railway and showed no response during the first 7 hours at an altitude of 14,110 feet. The usual response during residence at a high altitude consists of a rapid increase in the number of erythrocytes and percentage of hemoglobin during the first 2 to 4 days followed by a more gradual increase that requires several weeks and even months to establish equilibrium. Individual differences are always observed when a group of men is considered, as in the Anglo-American and the Bürker expeditions. A splendid set of observations that gives the typical curve is that of Richards (74) on himself, at 15,000 feet in Bolivia. In 5 days his hemoglobin increased from an average of 101 to 129 per cent on the Gower-Haldane scale; and then rose very gradually for 2½ months to 146. A residence of a few days to a week at the high altitude is not sufficient time for the changes to be completed. Schneider and Havens (82) observed two men who failed to respond in 4 days and others in whom the first changes were delayed 1 and 2 days. The men who were tardy in making these blood changes were fatigued by ascending on foot or were not in the pink of condition. The Anglo-American Pike's Peak expedition noted a distinctly low hemoglobin in three of the party the day following a fatiguing climb.

Theories on the mechanism of adjustment. Among the theories advanced to account for the increase in the erythrocytes and hemoglobin are: *a*, an increased concentration of the blood; *b*, increased hematopoietic activity of the bone marrow; *c*, the existence of a reserve or dormant supply of erythrocytes; *d*, a lengthening of the life of the erythrocytes (for which there has been no experimental evidence); and *e*, an unequal distribution of the red corpuscles.

Grawitz (41) early maintained that as a result of increased evaporation of water from the body the blood becomes more concentrated at high altitudes. Weiss (101) was unable to detect any alteration in the amount of hemoglobin per kilo body weight in animals at 4000 feet, even though the number of erythrocytes per cubic millimeter was increased. Jaquet (57), on the other hand, found in animals kept under a barometric pressure of 640 mm. of Hg. (5000 feet), that not only the percentage of the hemoglobin but also the total mass of hemoglobin increased; while the volume of blood remained practically unaltered. Abderhalden (1), working with animals at 6100 feet, concluded that the

amount of hemoglobin per animal was not altered, although the amount per kilo body weight as well as the percentage value of the hemoglobin and red corpuscles rose. The weight of his animals was uniformly less at the high altitude. He took this to indicate a concentration of the blood without over-production. Dreyer and Walker (24) believe that the change in blood volume is proportional to the area of the body surface. They recalculated Abderhalden's data and found that while the animals showed a diminished blood volume, yet the total amount of hemoglobin indicated a new formation; but they concluded that in animals examined during the first day or two after ascent the whole change was due to a diminution in the blood volume. Douglas, Haldane, Henderson and Schneider, by the carbon monoxide method of Haldane and Smith (46), determined the total amount of hemoglobin and the blood volume of four men during a residence of 5 weeks on Pike's Peak. They are of the opinion that three of their subjects had a diminished blood volume during the first days; but that afterwards there was a large increase in the total amount of hemoglobin and a return to, or even a slight increase above, the normal volume.

Other evidence of increased activity of the hematopoietic tissue has been forthcoming. Thus Zuntz, Loewy, Müller and Caspari (104) by a histological study of the bone marrow of dogs at sea level and at a high altitude showed a decrease in fat cells and an increase in the blood-forming elements in the animals acclimated to the high altitude. Dallwig, Kolls and Loevenhart (20) found an extension of the red marrow in animals under low oxygen, and a large increase of hemoglobin per kilo body weight. Laquer (63), working with dogs, found that if they were deprived of hemoglobin by a hemorrhage of half their blood supply, at sea level 27 days and on Monte Rosa 16 days were required to regenerate the hemoglobin. Schneider (78) proved there had been over-production of red corpuscles and hemoglobin by determining the changes after descent in a man who had lived 6 months at an altitude of 14,000 feet. In the course of 10 weeks the total oxygen capacity of the blood decreased about 12 per cent.

Schneider and Havens (82), from observations on the effects of abdominal massage and muscular exertion, concluded that a part of the first increase in red corpuscles and hemoglobin occurring with residence at a high altitude was brought about by the passage into the general circulation of a large number of red corpuscles that ordinarily are stored away. Their reasons were as follows: at low altitudes abdominal massage and physical exertion increase the number of erythrocytes

and percentage of hemoglobin in the peripheral capillaries; at high altitudes, before the blood changes of acclimatization have appeared, these still raise the content of hemoglobin and red corpuscle; but after men are partially or wholly acclimatized abdominal massage and exercise lower instead of increase their content. Recent work on the regulation of the volume and concentration of the blood has not favored this explanation. Scott (86) was unable to find masses of corpuscles stored away anywhere in the body and believes that the capillary blood is the same as that in the large vessels. Scott, Herrman and Snell (87) found an increase of the water content of the muscles during contraction and concomitantly with this an increased hemoglobin content and blood count. This passage of water out of the blood was associated with a rise in blood pressure. Lamson (64) also was unable to find a reservoir of red corpuscles of sufficient magnitude to appreciably influence the red count. He finds that all conditions of acute polycythemia in which there has not been sufficient time for red cell production are due to concentration of the blood by fluid loss, and that this loss from the circulation occurs through the liver lymphatics. While these more recent studies throw doubt on the explanation offered by Schneider and Havens, they do not account for the fact that after acclimatization abdominal massage and physical exertion not only failed to cause the usual concentration of the blood, but actually caused a decrease in the content of hemoglobin and the red cell count.

The mechanism by means of which the blood is concentrated has not been carefully considered with respect to altitude and low oxygen. That it is not chiefly the result of evaporation of water from the body as suggested by Grawitz is evident from the observation of Dallwig, Kolls and Loevenhart and of Gregg, Lutz and Schneider, in which men and animals were held under such conditions that perspiration and evaporation were normal or subnormal; furthermore Gregg, Lutz and Schneider obtained concentration within 15 to 20 minutes without any noticeable increase in the activity of sweat glands. Against the theory that it is chiefly due to an increased activity of the kidneys, as suggested by Birley (12) from observations on aviators, Gregg, Lutz and Schneider urge that the time in which concentration occurs, 15 or 20 minutes as seen in some aviators, is too short and the volume of urine eliminated too small. A study of the weight of subjects before and after experiment proves conclusively that the concentration cannot be due to a loss of water from the body. That it is not associated with the blood pressure is evident from numerous mountain,

low pressure chamber and rebreathing experiments in which the arterial pressures have not increased, but in some instances have decreased as the blood concentrated. The work of Bogert, Underhill and Mendel (13) and Scott, Herrman and Snell (87) show that in the regulation of blood volume the tissues act as the reservoir for excess fluid. Furthermore, as shown by Smith and Mendel (90) the excess of fluid may leave the blood as an exudate into the serous cavities or be excreted into the intestine and stomach.

The theory that the blood changes of altitude are due to an alteration in the distribution of the erythrocytes has had its chief support from Foa (34), who found that the ear veins of rabbits contained more red cells than the blood from an artery; and from Campbell and Hoagland (16) who found the blood from the mesenteries poorer in erythrocytes than that from the ear. Dallwig, Kolls and Loevenhart (20) later examined blood from the marginal ear vein and the carotid artery and heart and found the counts were the same within the limits of experimental error.

Undoubtedly the increase in hemoglobin observed, during short exposures to and during the early days at high altitudes, is largely or wholly due to a loss of fluid from the blood; while the permanent condition of acclimatization is the result of a new formation of red cells which finally restores the blood volume to normal.

Reasoning from the fact that his own erythrocytes did not increase during a short visit to Leadville and Pike's Peak at a time when his red count was abnormally high at sea level, Sundstroem (93) concludes that health in high altitudes is compatible with numbers of red cells that are normal for low elevations. The opinion is not in accord with some able clinicians. Sewall (76) considers anemia a dominant disorder at altitudes of 5000 and 6000 feet. He finds that failure to react normally to the altitude leaves the body in a mild grade of altitude anemia that originates or accelerates many functional disorders. Moleen (69) also finds much of the so-called altitude nervousness due to the failure of the hematopoietic response and that, if by therapeutic or other means the blood-forming mechanism can be stimulated into activity, individuals find no difficulty in living tranquil lives at high altitudes.

Variation in the size of the erythrocytes has been considered. Koeppe (59) found a decrease while Schauman and Rosenqvist (77) report a progressive increase in the diameter at high elevations. Sundstroem (92), (93) observed that in the same person on different occasions

there may be either an increase or decrease in the diameter and suggests that these alterations may be caused by, or correlated with, changes in the acid-base equilibrium of the blood.

Numerous attempts have been made to find nucleated red corpuscles but many have been futile. Schauman and Rosenqvist in experiments on animals found an increase of normoblasts and free nuclei. Gaule (39) from balloon ascensions gives doubtful descriptions of nucleated red cells and Sundstroem after much searching of his own blood found two characteristic normoblasts and a few free nuclei. Dallwig, Kolls and Loevenhart (20), working with animals kept under a low percentage of oxygen, showed that the number of basophilic erythrocytes was increased and that many of these were abnormally large. Such cells are indicative of excessive activity of the hematopoietic tissue.

Leucocytes and platelets. The number of white corpuscles is approximately the same at all altitudes (91), (92), but the differential count reveals a difference in the kinds of leucocytes. The outstanding feature is an increase in the large lymphocytes. The number of polymorphonuclear cells diminishes in exact proportion in which the mononuclear cells increase (91), (92), (99).

Comparatively little work has been done in connection with the blood platelets. Kemp (58) in 1903 found a tremendous increase at 14,000 feet. Webb, Gilbert and Havens (100) found that the platelet count at sea level as obtained from an average of counts made on one hundred college students was 302,000, and for one hundred men at 6000 feet was 340,000 per c.mm. No reason is known for this increase.

THE HEMATO-RESPIRATORY FUNCTIONS AT HIGH ALTITUDES. The whole problem of respiration at high altitudes is very closely linked with the control of the chemical reaction of the blood and, therefore, with the explanation of acidosis. Our interest centers about the balance of acids and alkalies because the absorption and unloading of oxygen by the blood is altered by variations in these. Carbon dioxide, by virtue of its acidic character, affects not only the respiratory center but also the dissociation of oxyhemoglobin; an increase in the partial pressure of carbon dioxide augments the dissociation, while a decrease causes the hemoglobin to hold more tightly to its oxygen.

It was early noted that the volume of air breathed is increased at high altitudes while the alveolar carbon dioxide pressure is lower than at sea level. To account for this increase in breathing Zuntz and associates (104) and Haldane and collaborators (14), (48), (98)

developed a theory that still persists, to a degree, among physiologists today; namely, that a deficiency of oxygen produces acids that are added to the blood. Boycott and Haldane (14) believed that the hyperpnea observed under want of oxygen is due to the formation of lactic or other acid substances and that these have the same influence as carbon dioxide on the respiratory center, so that less carbon dioxide is required to excite the center. That lactic acid does not accumulate in the blood, at least at moderately high altitudes, was proven by Barcroft, Camis, Mathison, Roberts and Ryffel (7), (8) in their expedition to Mt. Rosa.

Studies of the dissociation curve of the blood by Barcroft (7) and the Anglo-American Pike's Peak Expedition (23) have shown that, in the acclimated individual, the affinity of hemoglobin for oxygen is the same as at sea level, if the blood be exposed to a carbon dioxide pressure characteristic for the alveolar pressure of the altitude. This indicates that the carbon dioxide has been displaced by something which produces an equal effect on the affinity of hemoglobin for oxygen. If the blood of an altitude acclimated person be exposed to 40 mm. of carbon dioxide, the average alveolar carbon dioxide at sea level, the dissociation curve is displaced to the right, thus proving there has been an increase in acid radicals or a decrease in the bases of the blood. To account for these changes Douglas, Haldane, Henderson and Schneider suggested the theory that the adaptive regulation of the blood alkalinity is accomplished by a slight and gradual alteration in the exciting threshold of alkalinity for the kidneys, whereby they would slowly reduce the alkalinity of the blood and restore the acid-base relationship to that characteristic of acclimated persons. The stimulus for the slight alteration was assumed to be the presence of abnormal quantities of metabolites in the blood which had escaped oxidation in the lungs. This theory has recently been modified by Haldane (45) in view of more extended observations.

Y. Henderson and Haggard (44), (54) have used the carbon dioxide dissociation curve of the blood to show the amount of alkali in use in the blood. They find, with oxygen deficiency, that augmented breathing begins before a reduction of the blood alkali occurs; and that there is not a lowering of the blood alkali before or coincident with the increase in breathing, as was formerly taught. They find the hemato-respiratory events of acclimatization occur in the following order: *1*, a lowering of the oxygen tension of the inspired air; *2*, a stimulation of the respiratory center or, as they state it, an increased

production of respiratory x; *3*, excessive respiration and a blowing off of carbon dioxide; *4*, a decrease in the ratio of H_2CO_3: $NaHCO_3$, which means a lowering of the hydrogen ions, an alkalosis of the blood instead of the acidosis of earlier theories; and *5*, a compensatory disappearance of alkali from the blood. In complete acclimatization to any altitude the volume of air breathed is in inverse proportion to the amount of alkali in the arterial blood. Unquestionably the oxygen tensions in the lungs and arterial blood give the condition to which the organism adjusts its respiratory activity.

Haldane (45) explains these hemato-respiratory changes of acclimatization as follows: The hydrogen ion concentration of the blood is regulated with great delicacy by the respiration on the one hand and the kidneys and the liver on the other, the respiration doing the rough and immediate work by increasing or decreasing the elimination of carbon dioxide, and the kidneys the finer and slower work by adjusting fixed alkalies and acids. Oxygen want serves as an additional stimulus to the respiratory center, causing an increased amount of carbon dioxide to be washed out of the arterial blood. This loss of carbon dioxide makes the blood abnormally alkaline and causes the kidneys and liver to slowly redress the balance, the kidneys by excreting the excess of alkali and the liver by suppressing the accumulation of free ammonia.

The evidence in favor of the latest theory is the work of a number of laboratories. That the respiratory center is directly stimulated by oxygen deficiency is indicated by experiments of Gasser and Loevenhart (38) on animals and Lutz and Schneider (66) on men, in which they find that the hyperpnea may be excited by want of oxygen within 4 to 35 seconds, average about 14.5 seconds; a time too brief to make it probable that the stimulation is due to the accumulation of metabolites in the blood or the respiratory center. Haldane, Kellas and Kennaway (49) also conclude that oxygen deficiency *per se* can act as a stimulus to the respiratory center.

That there occurs increased breathing and a blowing off of carbon dioxide is clear from the alveolar air studies cited under our discussion of respiration. Theoretically the alveolar carbon dioxide is proportional to the carbon dioxide content of the blood. In addition direct measurements of the carbon dioxide content by Paul Bert (10) and Mosso and Marro (71) on dogs and by Sundstroem (92), by Van Slyke's method on himself, confirm the opinion that low oxygen tensions cause a loss of carbon dioxide from the blood.

In 1918, by simultaneous determination of carbon dioxide content and carbon dioxide capacity (which is a measure of the alkalinity) of the blood, Y. Henderson and Haggard (55) have shown that a decrease of the former is followed by a decrease in the latter, but that a lagging behind of the carbon dioxide capacity may occur. In a later paper they cite experiments made upon men by this method by Lutz and Schneider (44) in which the blood alkali during periods from 60 to 90 minutes of oxygen deficiency was not reduced, even though the carbon dioxide was reduced and the normal ratio H_2CO_3: $NaHCO_3$ was changed in the direction of a temporary alkalosis. Sundstroem (92), during the first two days of a sojourn at 14,110 feet, found the urinary excretion of base much less than later, while the hydrogen ion determination of the blood indicated an alkalosis.

That later the kidneys and liver restore the hydrogen ion content of the blood has been proven in several ways. Hasselbalch and Lindhard (53) found that the H-ions of the urine were reduced for several days and returned to normal only after acclimatization was established, and that the excretion of ammonia was also relatively decreased and continued somewhat low even after acclimatization. This latter condition Haldane (49) considers an evidence of a slight continuous alkalosis. By carefully constructing balance sheets of all the acid and basic elements in the food, feces and urine and thus obtaining the total acid-base balance of the body at low and high atlitudes, Sundstroem (92) at high altitudes found an increased output of base which consisted largely of fixed alkalies. He also obtained a decrease in the ammonia output which he explained as a corollary to the increased elimination of fixed alkalies. In this connection it should be noted that Macleod (67) has suggested that an excess of lactic acid in anoxemia may perform the function of neutralizing the relatively increased base. Sundstroem, however, found that excretion of lactic acid did not increase. Haldane, Kellas and Kennaway (49) have shown the titrable acids, as well as the ammonia, of the urine are much reduced during exposure to oxygen deficiency. These observations clearly indicate that it is the function of the liver and kidneys to restore the H-ion content of the blood resulting from the loss of carbon dioxide, and thus to give the final hemato-respiratory equilibrium of acclimatization. It is also evident that the total alkalinity, the alkaline reserve, is reduced in inhabitants of high altitudes.

There is a lack of agreement as to what maintains the greater ventilation of the lungs and the low alveolar carbon dioxide after acclimati-

zation. Barcroft (7) found that at any altitude the acidosis and diminution of carbon dioxide so nearly balance one another that the reaction of the blood remains practically constant; and yet, he has been able to show by a statistical study that there was a slight increase in acid over the sea level amount, and this he considered sufficient to give the respiratory center the slight stimulation which would account for the altitude increase in lung ventilation. Sundstroem, by an indicator method, finds a slight acidosis of the blood after successful acclimatization that lends support to Barcroft's position.

Hasselbalch and Lindhard (53) give a different interpretation. They find in acclimatization that the H-ion concentration of the blood is the same at all altitudes; and hold that the primary change is in the respiratory center, which becomes abnormally sensitive to the H-ions, resulting in increased breathing.

Haldane (45) is of the opinion that while after acclimatization the H-ions are again probably nearly the same as at sea level yet the restoration is never quite complete, so in the end there continues a slight alkalosis which gives evidence of a continued though slight oxygen want, and it is this that still permits action of diminished oxygen on the respiratory center. Henderson (44) believes that it is a low oxygen to alkali ratio that tends to stimulate respiration. Or rather, it is the low oxygen: alkali ratio which produces the respiratory x, that stimulates the respiratory center. He declares that it is not enough to say that oxygen deficiency is itself a stimulus or that it governs the excitability of the respiratory center for carbon dioxide, as these leave the question of how it does this unanswered. He, therefore, postulates an unknown substance, labeled respiratory x, that is formed by the action of the oxygen: alkali ratio.

During the early stages of adjustment to the low oxygen tension of high altitudes, the condition in the blood is favorable to a serious oxygen want. The loss of carbon dioxide from the blood should mean an increased affinity for oxygen. When the blood is in the lungs this would lead to a better absorption of oxygen than normally; however, when the blood is in the systemic capillaries the opposite is the case and this same affinity then prevents as free a passage of oxygen outward from the blood as normally would occur at lower altitudes. Therefore, until the liver and kidneys overcome the alkalosis of the blood the tissues of the organism suffer an oxygen want to a greater degree than they will later. The restoration of the normal hydrogen-ion content of the blood, in that it restores the oxyhemoglobin disso-

ciation curve to about its sea level value, must be regarded as an important factor in acclimatization.

Mountain sickness. The aviator, as has been previously pointed out, does not suffer from mountain sickness but simply from oxygen want. The degree appears to be determined chiefly by two factors, namely, the partial pressure of oxygen in the alveolar air of the lungs and blood, and by the degree of alkalosis of the blood. The latter as shown above affects the oxyhemoglobin dissociation by preventing the normal dissociation of oxygen and thus decreases the amount that passes to the tissues. The effects, as indicated by the recorded symptoms, appear to be chiefly caused by want of oxygen in the brain.

A complete explanation of mountain sickness has not yet been given. Without doubt it is chiefly due to anoxemia, so that such of the older theories as attribute it to mechanical causes and to the absence of carbon dioxide may be here neglected. Barcroft (7) believes that mountain sickness is caused by want of oxygen on the brain itself, but that the vomiting center is stimulated by the lack of acid in the blood. He points out that the symptoms of mountain sickness resemble those of a hemorrhage. As a preventive, he urges that acids be courted by physical exercise.

Y. Henderson and Haggard (44) believe that their postulated respiratory x may cause the symptoms of mountain sickness, in that it at first acts very much like ethyl ether in the excitement stage; while its later effects resemble the disagreeable manifestations of alcoholic intoxication.

Haldane, Kellas and Kennaway are unable to say to what extent mountain sickness is due to anoxemia or to the secondary diminution of the H-ions of the blood (alkalosis), but they believe the two causes are closely bound up together. Sundstroem states that it is possible that mountain sickness can be directly explained as a failure of the kidneys to respond sufficiently quickly to the excess of bases in the blood. He found an alkalosis of the blood during his attack of mountain sickness, and a normal H-ion concentration in the afternoon of the same day, when the symptoms of mountain sickness had entirely disappeared. Haldane, Kellas and Kennaway are of the opinion that good toleration of high altitudes is dependent upon the ability to quickly eliminate the excess of blood alkalies. The observations of Mosso (71) and of Hasselbalch and Lindhard (53) that the symptoms of mountain sickness were reduced by the inhalation of proper dilutions of carbon dioxide, and Barcroft's suggestion of courting acid, find a

satisfactory explanation in the theory that alkalosis is at least a secondary cause of the symptoms of mountain sickness.

THE CIRCULATORY MECHANISM AT HIGH ALTITUDES: *The heart rate.* The response of the heart to oxygen deficiency gives a good illustration of the fact that the behavior depends upon the suddenness and the extent of the changes in oxygen. Lutz and Schneider (66) by having men inspire nitrogen, obtained an acceleration of the heart in from 5 to 55 seconds, in 66 per cent of all cases within 15 seconds or less. In a low pressure chamber, in which the barometric pressure was lowered at a rate corresponding to an ascent of 1000 feet a minute, 26 per cent of all cases showed an increase at tensions of oxygen equivalent to an altitude of 4000 feet or less. In airplane flights the psychic influence of the excitement of taking off usually obscures the begining of the low oxygen effect, but Hodgson (56) has recorded several flights to 16,000 feet in which the typical low oxygen action is well illustrated. The experiments of Lutz and Schneider and the statistical study of Schneider and Truesdell (85) show that the heart rate slowly and gradually increases until the oxygen tension is about that of 14,000 feet, and from there on the increase is by much greater increments for each thousand feet of ascent. The increase averaged 15 beats at 15,000 feet and 20 at 18,000 feet.

Schneider (79), Lutz and Schneider (66) and Haldane, Kellas and Kennaway (49) observed that, if a constant level of low oxygen be maintained for an hour or more, the rate in many cases again retards, although in some there is a continued augmentation during the entire time of maintained level.

In the slow ascent of mountains which is followed by a sojourn of weeks or months the story is different. The early literature has been reviewed by Durig and Kolmer (26) and Schneider and Sisco (83). If the ascent be made passively by railway to 14,000 feet there is, as a rule, no acceleration during the ascent. What happens later appears to depend on the physical condition of the subject. If he compensate well to the altitude his pulse rate, at rest, will not show an increase for some hours; but by the next morning the rate, while in bed, will be slightly accelerated and continue to show a further increase each morning for from 3 to 5 days. In those less tolerant to altitude the heart accelerates as the attack of mountain sickness comes on, so the early morning rate may reach its maximum by the first morning. As the attack passes off the heart retards. In men who climb the mountain on foot or on a burro or horse, the fatigue of the climb

causes the pulse rate to resemble that in mountain sickness. The greatest augmentation occurs in men physically weak. The daily variations in pulse rate show the same proportionate increase as the early morning rate when compared with similar conditions at lower altitudes. While a number of authors have thought the pulse extraordinarily labile at high altitudes, Schneider, Sisco and Cheley (84) did not find it necessarily so. The heart works at an increased rate in all postures at high altitudes, with about the same differences as at the low altitude. The amount of increase, of course, differs with individuals, some show, at 14,000 feet, an augmentation of only a few beats; while others increase 10 or more over the low altitude rate.

During a prolonged sojourn at a high altitude the heart rate may show a gradual daily increase for about a week or two, but as other adaptive changes reach their maximum efficiency there is a tendency to return toward the low altitude rate (23). In only rare cases does it completely return to the low altitude normal.

The "after-effects" of a visit to a high altitude differ from those observed for respiration. After an exposure to oxygen deficiency for an hour or so the heart returns at once to its normal rate, but if the stay has been long enough for the permanent changes of acclimatization then the return to a low altitude may be followed by a subnormal rate. Durig and Kolmer (26), Schneider (78) and others (52), (92) have found a subnormal period that lasts many days. All observers agree that up to altitudes of 8000 or 9500 feet the acclimatized inhabitants do not show an altitude augmentation in heart rate.

The arterial pressures. The circulatory responses to oxygen deficiency as experienced during the short exposures in aviation have been the subject of a number of papers from Medical Research Laboratory of the Air Service of the Army (79), (66), (43), (64), (85). In a rapid ascent to 15,000 or 20,000 feet, if the psychic factor be not active, the systolic pressure in a good compensation remains unchanged or shows a slight gradual rise of not more than 10 or 15 mm. The diastolic pressure is also maintained to oxygen tensions corresponding to 15,000 feet and thereafter, as higher altitudes are attained, slowly decreases by about 8 to 10 mm. If the compensations to the low oxygen be inadequate the aviator is liable to develop a fainting circulatory reaction of which a rapid fall in the systolic and diastolic pressures gives evidence of the oncoming syncope. The various types of circulatory reaction have been described in detail by Schneider and Truesdell (85).

The arterial blood pressures of people living in the mountains have been made a frequent subject of study. The early literature has been reviewed by Schneider and Hedblom (81) and Durig and Kolmer (26). The conclusions of the Anglo-American Pike's Peak Expedition (23) and of Schneider and Sisco (83), who have examined a goodly number of men, are that the altitude effects in those who ascend the mountain passively are so slight that they fall for the most part within the errors of observation. In the majority of healthy men at 14,110 feet the arterial pressures were normal for them; in some there occurred a slight fall and in a few a slight rise. However, during an attack of mountain sickness and in some cases during the first days of inadequate compensation both the systolic and diastolic pressures are above normal.

Venous and capillary pressures. These pressures have not received much attention in anoxemia. Under the acute conditions of rebreathing and low pressure chamber experiments of from 25 to 45 minutes duration, the low oxygen reduced the venous pressure (80). On Pike's Peak, Schneider and Sisco found a lower venous pressure than at low altitudes. A few capillary pressure determinations with Lombard's device indicated that this pressure was slightly lower on Pike's Peak.

Volume of blood flow. This subject has been difficult to approach because of the lack of a satisfactory direct method of determining the per-minute output of the heart. The Anglo-American Pike's Peak Expedition concluded, from observations by means of a recoil board and from the pulse pressure, that the volume of the heart strokes continued practically the same on Pike's Peak as under ordinary barometric pressure. In one man, however, the heart stroke appeared to be somewhat diminished. The volume of the blood stream per minute in one subject was decidedly decreased, in another unchanged and in two others somewhat increased. Schneider and Sisco's records show that the pulse pressure averages slightly less on Pike's Peak, but that with two exceptions the difference is too small (2 mm.) to be significant. They believe that their recoil board records, along with those of pulse pressure, indicate that in four men the output per heart stroke was the same at both altitudes, but in another was reduced at the high altitude. Using Stewart's method of measuring the amount of blood flow through the hand, by determining the amount of heat given off in a water calorimeter, they found the circulation rate through the hands was, for six subjects, from 30 to 76 per cent greater on Pike's Peak. These observations, supplemented by those of the recoil board

and pulse pressure and the fact that the pulse rate had augmented, led them to conclude that the circulation rate as a whole was more rapid. Bainbridge (5) has pointed out that this increase in blood flow through the hands may be due to a dilatation of the limb-vessels counterbalanced by vasoconstriction elsewhere, presumably in the splanchnic area.

Hasselbalch and Lindhard (53), in six experiments in a low pressure chamber, at a barometric pressure somewhat under 12,000 feet, using a respiratory nitrous oxide method developed by Krogh and Lindhard, found a slight increase in the output of the heart in three of the tests. The fact that this increase was slight and that the flow was unaltered in the other experiments led them to conclude that the output of the heart is not increased at high altitudes during rest.

Kuhn (61), using the respiratory method of Plesch at an altitude of 11,000 feet, found that the output per heart stroke was decreased in two, unchanged in one and increased in the fourth man; while the per minute volume output of the heart was somewhat augmented in each subject (3.2, 5.8, 8.3 and 28.1 per cent).

Lutz and Schneider (66) find, in low pressure chamber experiments, indications of an increased blood flow in the augmentation in the rate of heart and in changes in the arterial pressures, which result in an increase in the pulse pressure. They also find that, when a constant level of oxygen is maintained, the heart rate may diminish and the pulse pressure again decrease. The interplay of the various circulatory factors throughout their experiments seems to support the theory of an increased blood flow during anoxemia.

That the volume of blood passing through the lungs during acute anoxemia, in an anesthetized cat, was the same as under ordinary atmospheric air has recently been demonstrated by Doi (105), by the use of a method in which the oxygen consumption per minute and the oxygen content of arterial and venous blood were determined. From the minute volume thus obtained he calculated that the output of each heart beat had decreased. Doi's findings are by means of a more direct method than others reported above and make it appear that the acceleration of the heart in anoxemia is a symptom of distress and not of compensation. This problem of the volume of the blood stream from the heart needs further study by these more direct methods under more natural conditions than obtain in the use of anesthetics. To the writer it does not seem likely that the acceleration of the heart which appears at the same time as the respiratory changes, in acute anoxemia, is merely a distress symptom.

Exercise. Physical exertion makes greater demands on the heart and blood vessels at very high than low altitudes. Just at what altitude this begins has not been investigated. Schneider, Cheley and Sisco (84) found that the arterial pressures were higher after a given form of work at the high than at the low altitude and that the influence of lowered barometric pressure was the more pronounced the more vigorous the exertion. The increased reaction to exercise was most conspicuous during the first days of residence. While the effects were lessened by acclimatization for moderate exertion, they did not show improvement in strenuous exercise The systolic pressure after short quick runs was as high as during a maximum lift of weights. Further evidence of greater exercise demand on the heart was that the delay in the return to normal was as prolonged as after exhaustive exercises. In physically fit men the influence of altitude in exercise was less.

Clinicians have found that as a rule the danger to the heart in high altitudes is overstrain from exercise and is not specifically due to altitude. Schrumpt (85) finds that up to 7,000 feet pathological blood pressures are improved. Zederbaum (103), Wyss (102) and others point out a fear of altitude among the laity and even medical men that is unwarranted; and show that altitudes up to 6000 or 7000 feet benefit many forms of heart disease.

Accepting then, for the present, only such factors as have been clearly demonstrated to serve in the compensation to anoxemia, we may rank them as follows: *1*, increased respiration; *2*, chemical alterations in the blood; and *3*, increased hemoglobin. The respiratory change ranks first because by this means the partial pressure of the oxygen in the lungs is raised above what it would normally be at the altitude. This favors not only the absorption of oxygen in the lungs but also, after acclimatization, the passage of oxygen from the blood to the tissues. Since the alkalosis resulting from augmented breathing interferes with the passage of oxygen from the blood to the tissues, it cannot be questioned but that the restoration of the normal H-ion content, by the elimination of the excess of alkali, constitutes a compensatory process of almost if not equal importance with the increase in breathing. The advantage gained by the increase in hemoglobin is not so obvious. Barcroft (6) finds the increase of but little value since even if it be sufficient to restore to normal the actual quantity of oxygen in 1 cc. of blood then, because of the decrease in oxygen pressure, the rate of dissociation will be so slow that it will not allow the oxygen

to pass to the tissues in anywhere near the same proportions. Haldane (49) considers the advantage of the increase in hemoglobin due to the fact that the partial pressure of oxygen in the blood of the systemic capillaries is prevented from falling as low as it otherwise would.

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